UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Relates To:** *Stokes et al. v. Johnson & Johnson Consumer Inc.*, 1:23-cv-11278 *Phippen et al. v. Johnson & Johnson Consumer Inc.*, 1:23-cv-11079 *Bordoy et al v. Johnson & Johnson Consumer Inc.*, 1:24-cv-693 *Day et al. v. Johnson & Johnson Consumer Inc. et al.*, 1:23-cv-11252 *Mota et al. v. Johnson & Johnson Consumer Inc.*, 1:23-cv-11074	Docket No. 22-md-3043 (DLC)

PLAINTIFFS' DISCLOSURE OF RULE 26 EXPERT WITNESS PURSUANT TO GENERAL CAUSATION DISCOVERY AND MOTIONS ORDER

Pursuant to General Causation Discovery and Motions Order (Doc. 391) and the Federal Rule of Civil Procedure 26(a)(2)(B)(iv-vi), Plaintiffs hereby disclose the following expert witness Roberta B. Ness, M.D., M.P.H., who may be called upon to provide expert testimony in the above-captioned matters. Plaintiffs further disclose that Dr. Ness specializes in the area of women's health and epidemiology.

1. Pursuant to the requirements of Fed. R. Civ. Pro. 26(a)(2)(B), the opinions Dr. Ness intends to offer and the bases and reasons for them are contained in her report, attached as **Exhibit A**. A list of materials Dr. Ness has considered and/or reviewed in forming these opinions, in addition to those cited in her report, is attached as **Exhibit B**.

2. Pursuant to the requirements of Fed. R. Civ. Pro. 26(a)(2)(B)(iv), attached as **Exhibit C**, please find a *curriculum vitae* outlining Dr. Ness' qualifications, including a list of all publications authored in the previous ten (10) years.

3. Pursuant to the requirements of Fed. R. Civ. Pro. 26(a)(2)(B)(v), attached as **Exhibit D**, please find Dr. Ness' deposition and trial testimony for the previous four (4) years.

4. Pursuant to the requirements of Fed. R. Civ. Pro. 26(a)(2)(B)(vi), Dr. Ness' hourly rate is $500 per hour for all work except in-person work including depositions, presentations, and testimony, which shall be billed at $1000 per hour.

Dated: February 7, 2024

Respectfully submitted,

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Exhibit A

Report on the question of whether acetaminophen causes ADHD in children exposed during pregnancy

Roberta B. Ness, MD, MPH

February 7, 2024

I have been retained to assess the degree to which the epidemiologic and other supporting literature supports a case for general causality between prenatal use of acetaminophen (APAP) and attention deficit hyperactivity disorder (ADHD). This report represents my expert assessment of the question: "Does acetaminophen use during pregnancy, within a reasonable degree of medical and scientific certainty, more likely than not cause ADHD?"

I am a former, tenured, full professor of medicine, obstetrics/gynecology, and epidemiology, and the Rockwell Endowed Professor in Public Health at the University of Texas at Houston. From 2008 to 2014, I was Dean of The University of Texas School of Public Health, one of the largest such schools in the nation, with over 1,300 masters/doctoral students and 500 faculty and staff on six campuses throughout the state of Texas.

I am a recognized expert in women's health and epidemiology. My book, *Health and Disease Among Women* (1999), established the leading paradigm in the field of women's health research, termed "gender based biology." Moreover, my approximately 450 peer review publications and 20 federally-funded grants cover topics including risk factors for cancer, pregnancy complications, and cardiovascular disease. My international accolades include membership in the exceedingly selective National Academy of Medicine, the most prestigious honorary society of physician-scientists in the United States. I have been inducted as a member in other prestigious honorary societies, including the American Society for Clinical

Investigation and Delta Omega Honorary. I am former president of the American College of Epidemiology and the American Epidemiologic Society. I am also a Fellow of the American College of Physicians, and associate editor or on the editorial board of numerous scientific journals. My other honors include a 1996 Leadership Award from the Family Health Council; 2006 Laureate Award from the American College of Physicians; 2008 Distinguished Professor of Women's Health from the Society for General Internal Medicine; 2013 Petersdorf Lectureship from the American Association of Medical Colleges; 2013 Snow Lifetime Achievement Award from the American Public Health Association; and 2014 Athena Swan Lectureship at Oxford University. In 2011, I was a U.S. Presidential appointee to the Mickey Leland Center for Environmental Air Toxicant Research. I have been an advisor to the National Institutes for Health, the Centers for Disease Control and Prevention, National Academies of Science, and the Department of Defense, among other agencies. In 2017, I won the highest lifetime achievement award in my field, the Lillienfeld Award. In 2022, I was recognized as one of the world's Best Female Scientists by the highly respected website, Research.com, based on the over 35,000 citations of my publications, as well as my awards and achievements.

I received my MD from Cornell University and my MPH in epidemiology from Columbia University. My education, training, and experience are set forth in greater detail in my Curriculum Vitae which is attached. I am compensated at the rate of $600 per hour for my work on this case and $1000 per hour for any time during deposition or trial that I am at the venue and working.

An analytical review and evaluation of the published literature along with my education, training and experience provide the basis for my opinion. The methodology I used with regard to assessing general causation incorporates a set of characteristics suggested by Sir Austin Bradford Hill in 1965 to describe the conditions needed for epidemiologic studies to establish

causality (Hill 1965) and since adapted and used in reports issued by many scientific agencies, such as the International Agency for Research on Cancer, Environmental Protection Agency, National Academies of Science.

Bradford Hill Criteria

Hill's tenets for consideration of causality include: 1) strength of association; 2) consistency; 3) specificity; 4) temporality; 5) biologic gradient (dose-response); 6) biologic plausibility; 7) coherence; 8) analogy; and 9) experiment. Consistency and temporality are often considered to carry particular weight by epidemiologists with whom I have collaborated (notably I have been president of two of the three major societies of epidemiology and so have had many and ample opportunities to discuss this). Experimentation—in particular a randomized controlled trial—is the gold standard for establishing causality, but for reasons discussed below, the association between APAP and ADHD has never been studied and likely never will be studied in a clinical trial. Therefore, cohort studies are the best design available to assess causation here.

Each of these will be considered at the end of my report, after a review of contributing studies. In addition to these core considerations, as suggested by leaders in the field of epidemiology, I will discuss the possibility that an observed association is not real but instead non-causal or even spurious because it is contaminated by systematic errors including bias and confounding. (Glass 2013)

As noted in one influential review, "[t]he Bradford Hill Criteria remain one of the most cited concepts in health research and are still upheld as valid tools for aiding causal inference." (Fedak 2015)

Researchers employ Hill's criteria in accordance with Bradford Hill's recommendation regarding how to decide "that the most likely interpretation" of an association "is causation." Hill explained his methodology and offered the following nine (non-exclusive) elements – none of which, except temporality, is individually necessary to make a causal inference – but instead are employed in aggregate and based on expert judgement, after a complete and systematic review of the literature.

Strength of Association

The greater the magnitude of the association between the exposure and the outcome, the more likely a causal relationship exists. "A strong association can help to rule out hypotheses that the association is entirely due to confounding or other bias." (Rothman 2008) Bradford Hill cautioned that this factor is not always determinative, because there are relationships that are truly causal but not large in magnitude. As he put it: "[W]e must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so." As a result, there is "no general rule for how large an association needs to be to meet this consideration," and attempts to require "sharp boundaries," "such as at a doubling of risk" are based on "fallacious arguments," which should not be followed. (Hill 1965)

Thought leaders in the field of epidemiology, including Ken Rothman, former editor of the journal *Epidemiology* and author of two the most influential textbooks in the field: *Modern Epidemiology* and *Introduction to Epidemiology*, noted "there are many weaker associations that are generally agreed to reflect causal effects," including the link between "air pollution and mortality," "smoking and heart disease," and "environmental tobacco smoke [*i.e.*, secondhand smoke] and lung cancer." (Rothman 2008) Although relatively weak, these associations "are considered

causal in part because they have been replicated in a variety of populations using different designs and in part because considerations other than strength," i.e., the other of Hill's factors.

Although some have asserted that an odds ratio ("OR") of 2.0 or more should be required before making a causal inference, that set-point is arbitrary and represents no important clinical or biological reality. Presumably, it is a legal surrogate for the need to prove that it is more likely than not that exposure X causes outcome Y in an individual patient, in the absence of a differential diagnosis or differential etiology analysis. However, the case specific criterion for whether or not an individual person's disease is "more likely than not" caused by an exposure is not equivalent to an OR of 2.0 – the former representing a reasonable degree of scientific certainty based on Hill's tenets and judgement, while the latter represents a numeric doubling of risk. These are completely different concepts. It is true that the larger the effect size, the less likely it is to be subject to bias and confounding, but there are many cases wherein poor study design has led to consistently large risks that turned out to be spurious (e.g., Vitamin C and Vitamin E were protective for endpoints in early observational studies but not in later clinical trials). (Jha 1995) The converse is also true – there are many modest associations now accepted as causal (see below). To scientists and clinicians, an association of modest size demonstrated in well-conducted studies and found with excellent consistency is considered far more convincing than stronger, less consistent links from poorly conducted studies—even if some of the risk ratios are high.

Examples of associations in the range of 1.3 to 1.6 follow. Notably, in each of these situations, these modest associations were accepted as causal by the epidemiologic community, changed clinical opinion, and altered public health practice.

Example 1: Occupational exposure to Benzene and risk of leukemia: In 2010, a meta-analysis of 15 epidemiologic studies found that worksite benzene exposure increased risk of any leukemia by 40% (relative risk 1.40, 95% CI 1.23–1.57). (Khalade 2010) On the basis of this literature and support, benzene is considered a cause of leukemia and is regulated as such.

Example 2: Post-menopausal hormone therapy (HT) and breast cancer risk: The Women's Health Initiative clinical trial showed that HT increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of the risk that HT causes breast cancer and other adverse events (HT was associated with a 29% increase in coronary heart disease, and 41% increase in stroke). (Rossouw 2002) A meta-analysis of clinical trials and observational studies in 2018 found that use of this therapy increased risk of breast cancer by 59% (relative risk 1.59, 95% CI 1.40–1.81). (Kim 2018) These results led to FDA-required label warnings on estrogen and progesterone therapy preparations, and to clinical warnings against use of estrogen plus progesterone for prevention of chronic conditions. (Grossman 2017)

Example 3: Trichloroethylene and risk of kidney cancer: In 2012, a meta-analysis was published showing that occupational exposure to trichloroethylene was associated with an approximately 30% increased risk for kidney cancer (relative risk 1.32, 95% CI 1.17–1.50). (Karami 2012) This and other evidence resulted in trichloroethylene being reconsidered by IARC, which then deemed it Group 1: carcinogenic in humans.

Example 4: Talc and ovarian cancer: The elevated risk from talc use is an 8% to 30% excess risk as indicated by several meta-analyses. For example, a pooled hazard ratio (HR) from cohort studies was 1.08 (0.99–1.17), on the edge of statistical significance. The HR for women

with a patent tract was 1.13 (1.01–1.26). (O'Brien 2020) Also, Taher (2018) included 27 studies, three of which were cohorts and reported an overall estimate for perineal use of talc of 1.28 (1.20–1.37) in relationship to ovarian cancer. There was no evidence of heterogeneity and study quality did not substantially impact the estimates. Penninkilampi (2018) reached a similar result with 24 case-control studies and 3 cohorts. The overall estimate for perineal talc use in association with ovarian cancer was 1.31 (1.24–1.39) with no evidence of heterogeneity. Based on these results, J&J removed talc from all U.S. baby powders in 2020.

Example 5: Air pollution: exposures that are common, even though their association is modest or even "weak" can cause large numbers of cases. The World Health Organization (WHO) estimates that as many as 99% of the world population breathes air that exceeds WHO air quality limits. Because a large proportion of the population is exposed to the risk factor, even a small increase in risk can result in a large number of people suffering from fatal diseases or conditions in excess to those who would have suffered in the absence of the exposure. The Lancet commission on air pollution and health estimated that air pollution caused 9 million deaths globally in 2019. (Landrigan 2018) Yet, air pollution has a weak association with the risk of death. The most definitive meta-analysis of air pollution and death reported a relative risk of 1.06 (RR = 1.06, 95% CI = 1.05–1.07) for an increase of 100 μg/m3 increase in total particle concentrations in ambient air. (Schwartz 1994) A relative risk of 1.06 indicates that there is only a 6% increase in the risk of death associated with the exposure. Most people globally are exposed to air pollution, thus, this small excess risk associated with air pollution results in tremendously high numbers of deaths globally.

In sum, exposures that are small can be causal. When common, such exposures can have a significant impact on public health. It is important to consider both the relative risk and the prevalence of exposure when assessing its impact on the population. In the case of prenatal

acetaminophen (APAP) exposure and childhood attention deficit hyperactivity disorder (ADHD), both exposure and outcome are common. Thus, even a small elevation in risk would impact many children and have large economic and social effects.

Consistency: "A consistent finding is an association reported across multiple populations, over time, and using different study designs." (Rothman 2008) Such associations support a causal inference. In other words, "[h]as [the association] been repeatedly observed by different persons, in different places, circumstances and times?" (Hill 1965) Traditionally, Hill's consistency criterion is upheld when multiple epidemiologic studies, using a variety of locations, populations, and methods show a consistent association between two variables with respect to the null hypothesis. In addition to human epidemiology, more basic research can be used in coordination with the results of observational studies to demonstrate consistency. "Nonetheless, consistency across studies of a similar design helps rule out chance as an explanation for an observed association." (Rothman 2021)

Notably, a set of results can be consistent even if some of the results are not statistically significant. The important question revolves around whether point estimates (relative risk (RR), hazard ratio (HR) or odds ratio (OR)) are consistently above 1.0. The better the quality of the study, the greater the weight an epidemiologist imparts to the point estimate. So, if the best studies are almost all positive (risk estimate above 1.0), this implies consistency. Although "it is sometimes claimed that a literature or set of results is inconsistent simply because some results are 'statistically significant' and some are not," this reasoning is "completely fallacious." (Rothman 2008)

Biological plausibility:

The existence of a biologically plausible mechanism to explain the association between the exposure and the outcome supports, but is not required to find, a causal inference. To establish biological plausibility, researchers look at "not only epidemiology," but also "other human studies, animal and tissue studies, and currently understanding of the biology, pathology, toxicology, and other mechanisms related to the effect." (Rothman 2008) Bradford Hill noted that it was not possible to "demand" this feature, because "what is biologically plausible depends upon the biological knowledge of the day." (Hill 1965) As he recounts, true causal relationships (for typhus and rubella) were once ignored and doubted because the biological mechanism was not well understood at the time.

*Temporality. "*Temporality means that a cause must precede its effects, and this is a necessary condition for valid causal inference." (Hill 1965) That is, the exposure must precede the outcome in time: "which is the cart and which the horse?" (Hill 1965) This criterion is typically used to rule out "potential reverse causation," (Rothman et al. 2021) whereby the outcome leads to the exposure. For example, the number of umbrellas on a street is strongly correlated with whether it is raining, but the presence of the umbrellas does not cause the rain. Prospective cohort studies typically reduce the risk of reverse causality because exposure is measured in real-time before disease occurs, but do not entirely preclude it. In the case of APAP and ADHD, prenatal use clearly precedes ADHD diagnosis, which rules out true reverse causation. But the other question for temporality is whether fetal exposure to APAP occurs prior to or during the stage of neurodevelopment when disruption could plausibly cause ADHD.

Case-control studies, because they rely on recall, do not preclude reverse causality. In a case-control study, subjects already diagnosed with disease report previous exposures. This retrospective characteristic of the design makes it possible that the ADHD diagnosis differentially influenced the reporting of the use of APAP. As just noted, however, for both cohort

and case-control designs, I will consider the question of temporality based on the known biology of timing of exposure vs. timing of the critical window of neurodevelopment. And as detailed below, most of the studies in this literature are prospective cohort studies, not case-controls.

Specificity

This criterion denotes that exposure is uniquely linked to one and only one disease. Specificity of an association can refer either to a cause having a single effect or an effect having a single cause. For example, a particular bacteria can cause a pathognomonic infection (*M. tuberculosis* causes tuberculosis, *T. pallidum* causes syphilis). Fewer examples are found in chronic diseases - even for the most compelling causal association in cancer, smoking and lung cancer, there is no specificity. Tobacco smoking is associated not only with cancers such as mouth and throat, voice box, esophagus, stomach, kidney, pancreas, liver, bladder, cervix, colon and rectum, and leukemia, among others, but also with non-cancer outcomes such as heart disease, stroke, lung diseases, diabetes, and chronic obstructive pulmonary disease (COPD), respiratory infections, certain eye diseases, and autoimmune disease. Meanwhile, each of these diseases has many other causes. Despite its lack of specificity, tobacco smoking is considered causally related to lung cancer.

Few if any cancers have a single cause and few toxicants cause a single outcome. When the exposure is associated with a specific outcome, causality is more strongly supported. In contrast, a non-specific association is one in which the exposure is associated with multiple outcomes, or the outcome is associated with multiple exposures. Bradford Hill cautioned that one should not "over-emphasize the importance of [this] characteristic." (Hill 1965) Hill expressly offered his opinion that "one-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor. In short, if specificity exists, we may be able to draw conclusions

without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence." (Hill 1965) Scientific developments since 1965 have shown Hill to be correct. "[I]ndeed, many behavioral, environmental, social, and genetic risk factors have been linked to more than one health outcome," meaning that even in situations of known causality, specificity is not satisfied. In part for this reason, under modern approaches, "[t]he original criterion of specificity is widely considered weak or irrelevant from an epidemiologic standpoint." (Fedak 2015)

Biologic gradient or Dose-response

Demonstration of dose-response provides particularly powerful evidence of causation when it is present. As Bradford Hill notes, "the fact that the death rate from cancer of the lung rates rises linearly with the number of cigarettes smoked daily adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers." (Hill 1965) A "clear dose-response curve" puts the case for causation "in a clearer light." (Hill 1965) Evidence of a linear increase in cases with greater duration and amount of exposure is the most common evidence of a biologic gradient. Not all exposures act in a linear manner. In some situations, an inverse proportion is observed: greater exposure leads to lower incidence. Although a monotonic biological gradient provides the clearest evidence of a causal relationship, even a "nonmonotonic dose-response association" does not "refute causation" as "many substances display u-shaped or j-shaped dose response effects." (Rothman 2008)

To calculate dose appropriately and fully, the following formula is applied: degree of exposure = duration x amount (frequency x dose or concentration). In many situations, only duration, only frequency, or only concentration is available, and each of these are used individually as a surrogate for degree of exposure. In aggregate, these individual measures can be used as a surrogate for dose. That is, when duration, frequency, and concentration all suggest a dose-

response, this is accepted by epidemiologists as an acceptable proxy for dose response as defined by duration x amount.

Analogy

Analogy refers to comparison to any other known toxicant that acts by a mechanism similar to the putative mechanism for the exposure of interest and is accepted as an established cause of that outcome. According to Rothman, “Analogy refers to drawing inferences about the association between a given exposure and disease based on what is known about other exposure-disease relations. For example, based on what is known about the health effects of cigarette smoking, we might expect that inhalation of other combustibles (e.g., marijuana) would have similar effects, even in the absence of studies on the subject.” (Rothman 2008, p 21)

However, sometimes drugs that are expected to act similarly - even drugs within the same class of medications - actually have disparate effects. Meanwhile, there are often causal relationships that exist in the absence of obvious analogies, because whether an appropriate analogy exists “is limited by the breadth of knowledge and imagination of the scientist” and not necessarily “the falsity of the [causal] hypothesis.” (Rothman 2008, p 22)

As a result, the criterion of analogy strengthens the case, but is not a requisite for causality. As per Bradford Hill, “With the effects of thalidomide before us, we would surely be ready to accept slighter but similar evidence with another drug . . . in pregnancy.” (Hill 1965) Thus, finding a drug that works through the same putative biologic mechanism as APAP and is established to cause ADHD when administered prenatally would strengthen the case for APAP causing ADHD.

Coherence

Coherence considers the totality of the literature. Rather than asking the positive question: “is the interpretation of the data in keeping with the epidemiology, natural history and biology of the disease, it asks the negative question. The definition of coherence, adapted from Hill by Thomas Frieden, Director of the Centers for Disease Control (CDC), and others at CDC in a recent editorial is: “Does the cause-and-effect interpretation of the association ‘seriously conflict’ with ‘generally known facts about the natural history and biology of the disease?’” (Cogswell 2016) This does not imply that biologic plausibility is necessary or sufficient to establish coherence. Hill himself commented on coherence when he noted, regarding lung cancer, “Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man.” (Hill 1965)

Experiment

Experimental studies in pregnant women, i.e., clinical trials of APAP use, have not been undertaken and almost surely will not be in the future. The benefit of experimental studies is that because they allocate exposure randomly between groups, they avoid a good deal of confounding and bias (see below for definitions of these). However, such research in the situation of prenatal APAP is untenable. Randomizing women to APAP use during pregnancy would be unethical if it were to involve asking non-using persons to use the medication to determine if it is hazardous to their fetuses. This is particularly true since observational data (reviewed below) suggests that such exposure may be hazardous to the unborn child. An alternative design would be to require women already taking APAP for fever or pain to entirely avoid usage. This would, again, be unethical since APAP may be an appropriate treatment for

certain conditions in pregnancy including fever. It would potentially put fetuses at risk of damage from uncontrolled fever. Even if an alternative analgesic or fever/pain lowering strategy could be found to replace APAP, analyses would end up with an admixture of women randomized to non-use who had not complied, and women assigned to non-use who had complied, resulting in misclassification that would dilute the observed effect. Since conduct of a randomized clinical trial does not exist and is out of the question for future conduct, it is, by definition, not satisfied as a Hill causality tenet.

Summary

Sir Bradford Hill made clear that most of the factors above are not individually required to be satisfied before a researcher can reach a causal inference. “Hill’s nine aspects of association were never intended to be viewed as rigid criteria or as a checklist for causation.” (Fedak 2015) And “Hill also emphasized that causal inferences cannot be based on a set of rules” but instead must be done in a manner “more akin to clinical judgment.” (Rothman 2008)

Specificity is rarely met in the situation of causal relationships. Similarly, analogy is supportive when it occurs but is not required. Strength of association can be modest and support causality. Biologic mechanism is often (even typically) unknown; that criteria requires a plausible, not an established, mechanism. Only temporality, is “indeed necessary (*a sine qua non*) for causal explanations of observed associations.” (Rothman 2008) This is “perhaps the only criterion which epidemiologists universally agree is essential to causal inference.” (Fedak 2015) Other than this, there no necessary and sufficient elements for determining causality. The evidence must instead be judged across all criteria.

It is important to note that establishing causality is complex and requires not only careful consideration of the above factors, but a weighting of the quality of evidence and consideration

of systematic error—i.e., the potential for chance, bias, and confounding. The purpose of applying Hill's tenets is "To determine, based on all of the data," where there is "any answer equally, or more, likely, than cause and effect." (Hill 1965)

Overarching considerations in the assessment of epidemiologic studies

Observational designs strengths and weaknesses:

Prospective cohort studies involve passive collection of data over time; there is no intervention by investigators. Experimental methods such as randomized clinical trials involve the researcher actively manipulating exposures, but as noted above, are irrelevant for the question at hand. Two types of observational studies have been employed in assessing the relationship between prenatal APAP use and ADHD: cohort and case-control.

In cohort studies on prenatal APAP exposure and ADHD, APAP use is ascertained at the onset of observation or sometime during pregnancy. The study ends when the resultant child is later diagnosed with ADHD or the period of observation is over. After that specified period of follow-up, the proportion of children developing ADHD is compared among those exposed *in utero* versus the proportion unexposed. This is called an ever/never comparison. Other possible comparisons include exposure in specific trimesters, duration of exposure, or exposure concentration. Associations are expressed as a Relative Risk (RR) or Hazard Ratio (HR). Both expressions represent the calculated risk of children developing ADHD among those exposed as compared to the risk of developing ADHD among those unexposed.

Cohort studies have the advantage of ensuring that the exposure preceded the disease and thus generally preclude recall bias. Because the woman reporting APAP exposure cannot predict whether her child will/will not be affected by ADHD in the future, she would be unable to

differentially report APAP use based on future ADHD diagnosis. However, non-differential misclassification is a major concern in APAP studies. Non-differential misclassification occurs when a random group of mothers (independent of the eventual ADHD status of their children) underreport APAP use, a situation that is likely common (discussed in detail below). Differential misclassification, as in the scenario of over-recall of APAP use among mothers with ADHD children, tends to overestimate observed effects. (If mothers with ADHD children systematically under-recalled APAP use, that would underestimate the observed effects.) Non-differential misclassification tends to underestimate observed effects, a phenomenon called bias toward the null.

Said another way, if exposures are biased by knowledge of outcome, as they may be in case-control designs (see below), they may overestimate any real effect. The opposite concern is common in cohort studies. Since all individuals may have faulty recall for medication use, and particularly for non-prescribed, over the counter (OTC) medications, the resulting RR may underestimate any real effect. (See below under *Exposure Misclassification* a more complete discussion.) This is because if both those with and those without the outcome of interest simply report less exposure, then the study result will be diluted and will find that there is less of an association. Since women often consider such OTC APAP use to be insignificant, as addressed below, cohort studies may spuriously underestimate real associations.

Finally, cohorts involve all subjects willing to participate in the research. Commonly, this is thought to eliminate selection bias. But, as discussed below, that assumption does not always apply. There is no selection of who is invited to be involved, reducing the risk of selection effects (bias) (see below *Bias)*. These advantages suggest that the validity of the results from cohort studies are higher than other observational designs. Thus, in the hierarchy of observational designs, cohort studies are typically listed at the top.

However, cohort studies have limitations as well. They must be large enough to, at least theoretically, establish statistically significant associations. The epidemiologic term for eliminating an error of omission is power. Power is the statistical likelihood of finding (not overlooking) a real association that exists. Typically, studies with at least an 80% probability of avoiding overlooking a real association are considered valid, but clearly the larger the sample size, the more likely they are to find a sizeable number of children with ADHD and the larger their power.

Another limitation in the number of cohort studies able to validly detect an association between APAP and ADHD is the lengthy period of follow-up necessary to establish the outcome among all susceptible children. Symptoms of ADHD often do not arise until children are school age. Data from the CDC indicates that the prevalence of diagnosed ADHD is 2% among 3–5-year-olds, 10% among 6–11-year-olds, and 13% among 12–17-year-olds.

Case-control studies compare cases with disease to controls without disease. For studies examining the effect of prenatal APAP use on later ADHD diagnosis in the child, only the Chen (2019) study employed a case-control design and that was nested within a registry (cohort) database. As such, many of the concerns discussed here do not apply (see Chen critique) but are presented here for context and completeness. Case-control studies use as their metric of association the odds ratio (OR), that is the odds of a case being exposed versus a control being exposed. In the present discussion, this is a comparison between the likelihood that a child diagnosed with ADHD would have been exposed to APAP vs. that a child without ADHD would have been exposed.

In contrast to cohort designs, case-control studies are well-suited to rare outcomes with long latency periods because their collection of data on exposures begins when persons have already developed disease. Cancer studies often rely on case-control designs. However, this methodology is subject to more biases than cohort studies. These biases include recall bias and selection bias, both of which can inflate or deflate the observed effect.

Recall bias inflates the apparent effect when it is differential (more evident among cases than controls) and thus away from the null. This differential misclassification can create a spurious association, i.e., finding a risk when none really exists. However, just as poor memory can affect cohort studies, it can also affect case-control studies. Non-differential forgetting biases results toward the null.

In the situation of APAP use, potential toxicity has not been a concern that entered the public sphere until the past year or so. All case-control studies on APAP and ADHD were conducted prior to that time frame. Thus, differential recall bias is unlikely to have affected study results. If it were operant and if mothers with ADHD children over-reported APAP used during pregnancy, this would be a situation of non-differential bias that would inflate the observed risk. Because, even in the Chen (2019) study, APAP use was recorded independent of ADHD status, non-differential bias remains the primary major concern. Thus, differential recall bias is not emphasized in the studies reviewed below. Instead, exposure misclassification for APAP is the relevant concern and would not inflate observed risk, but instead reduce observed risk.

To understand non-differential misclassification bias, consider an extreme scenario in which 100% of women in a particular study actually used prenatal APAP. However, let’s say that only 50% reported APAP use. Let’s also assume that the risk of a child developing ADHD because of exposure is 3-fold. Comparing the half of subjects who denied use to the half who reported use

would compare two groups with the same exposure characteristic (all exposed). Despite the large elevation in actual risk, there would have been *no* observed difference between groups since in actuality all were exposed. That is, the true risk was 3.0. The observed risk was 1.0. Non-differential misclassification diluted, indeed eliminated, the true effect.

Another bias of concern in case-control studies is selection bias. Cases are typically garnered from registries or hospital/clinic records. In the best designs, controls come from the same registries or facilities as cases or from the underlying population from which cases arose. Nonetheless, selection bias arises because it can be difficult to define the best groups of individuals constituting controls. For instance, cases may be more willing to participate in research. Controls may have fewer behavioral risks, or they may have more behaviors that promote the development of cancer. Use of such controls would lead to differential bias away from the null. The effect could be to inflate the observed estimate, or it could be to deflate the observed estimate. Hospital controls are particularly difficult to select. An obvious example might be the following: a study of smoking and colon cancer uses patients with COPD as controls. Both colon cancer and COPD are increased among smokers. Because the controls include many smokers, any effect that smoking may have had on colon cancer is diluted. The converse is also possible. Testing the same hypothesis that smoking increases colon cancer, a study drawing controls from Utah where members of the LDS church live, would likely reach a result that is inflated since that religious denomination has relatively low rates of tobacco use.

To overcome this selection problem, population-based cases and population-based control selection is generally considered superior to hospital control selection. Fewer decisions must be made on the part of investigators when taking controls randomly from the population, thus population-based case-control studies are generally considered less biased than hospital-based designs.

Exposure misclassification:

Many studies of APAP use during pregnancy have relied on memory for the measurement of APAP use, the primary exceptions being Baker (2020), Ji (2018), and Ji (2020). In general, the cohort studies (or case-control studies nested in cohorts) were designed to look at a large variety of exposures and outcomes, not specifically for the purpose of examining the potential toxicity of prenatal APAP use and so did not ask the specific question, “did you use acetaminophen? At what strength, when, how often, and for how long?” Instead, studies often asked about the use of analgesics in general as part of a larger medication list and then had subjects specify, or they asked about use of medications and then asked for these to be listed, or they listed indications and then asked what the woman took. Such approaches allow for reporting of a wide array of medications, but they do not trigger recall as clearly as a series of direct questions. Individuals who did not consider OTC medications to be relevant or memorable may not have reported use. Studies using checklists in which analgesics were specifically queried by name would have resulted in a more complete exposure profile than open-ended questionnaires, but in the literature overall, there is almost certainly a systematic underreporting as discussed below. This would have resulted in non-differential misclassification and a bias toward the null, i.e., an undervaluation of the risk.

OTC medication use is typically more poorly recalled than prescription medication use. Dolja-Gore (2013) assessed the agreement between self-report by mail and pharmaceutical claims data for a variety of medications. The authors accessed a national sample (N = 4687) of older women aged 79 to 84 conducted in 2005 in Australia. Common medications used among older women were selected, for retrieval periods from pharmaceutical claims data of three and six months. Both for six-month retrieval and for three-month retrieval, Kappa statistics of agreement, which measure the degree to which the two results concorded, were lowest for the

two OTC medicines ascertained: 0.35 for aspirin and 0.48 for folic acid in the most recent three month, and 0.50 and 0.60 for agreement in the most recent six months. In contrast, medications available by prescription only and not dispensed OTC were associated with Kappas of 0.75-0.93. Clearly, then, OTC medications were substantially more poorly recalled than other drug classes, and, indeed, were generally remembered no more often than chance.

Other studies have reached similar conclusions. One reported an investigation of the influence of mental, physical, and socioeconomic factors on medication recall, factors on self-reported medication use. The analysis was based on the Survey of Health Aging and Retirement in Europe (SHARE) (n = 77,261 participants aged a mean of 68.47 years). Depression, memory function, and polypharmacy had a particularly strong influence on the self-report of medications taken for “diseases of the stomach or ulcers” than many other indication categories. (Schönenberg 2021)

For analgesics, also typically bought OTC, another study suggested that women did not consider their use worth mentioning or did not consider these as medications. A survey among a general population sample of Danish women asked them to list their medications. Only 26% reported analgesic use. Women were then followed-up and asked specifically about analgesics. Over half of respondents, which is an additional quarter of subjects, then reported analgesic ingestion. Poor recall of OTC medications such as APAP suggests that self-report likely resulted in substantial non-differential exposure misclassification and bias toward the null.

Exposures categorized as ever/never almost surely underestimate true risk. Such studies aggregate individuals with long duration and/or high dose use and individuals with only minimal exposure. It is easy to see why such categorization would underestimate any true risk. (Rothman 2008) Comparing recall with a biologic measure of APAP exposure makes this point.

(Laue 2018) The GESTation and Environment (GESTE) study recruited 238 pregnant women during their first trimester and assessed APAP use as a yes/no question and exposure during labor using medical records. They then measured concentrations of APAP in meconium (baby's first bowel movement, which concentrates chemical exposures during the second two trimesters) using ultra performance liquid chromatography tandem mass spectrometry. Meconium is produced by the fetus starting in the early second trimester of pregnancy. It is widely considered a valid and more sensitive measure than self-report for *in utero* exposure in the final two trimesters of pregnancy (Baker 2020, Ostrea 2006, Delano 2019, Lange 2014) Acetaminophen administration during labor was associated with a significant increase in meconium APAP concentration (p=0.0002). However, self-reported intake during pregnancy was only marginally associated with meconium concentrations (p=0.10), adjusting for administration at delivery. Assuming that use of APAP was relatively consistent during the first and later trimesters of pregnancy, this suggests that ever/never report of an OTC drug exposure may have been substantially misclassified and resulted in an underestimate of effect.

To calculate doses requires knowing the strength and amount of use, as well as the duration of use. Classically, the formula for dose is: amount (strength x frequency) x duration. Lack of data on amount or on duration typically biases results toward the null. That is because, for instance, patients taking APAP several times a day would have been mixed with those using it only once a day. Moreover, without data on dose, those taking one regular strength (325 mg) could not be distinguished from those taking two extra strength (500 mg each, 1000 mg total). Finally, if duration is not known or known only crudely, dose estimation may be substantially limited. In all situations of missing information, the actual dose would not be known. The impact from high dose/heavy use would be diluted by lower dose/lighter use. Since the data would be missing equally in those exposed vs. not, or in those with the relevant condition vs. controls, the result would be non-differential misclassification and an underestimate of the true risk.

Other “hard” exposure ascertainment methods, in particular pharmacy records, which were the basis for categorizing exposure in the Chen (2019) study, may have resulted in similar or even worse misclassification. Pharmacy records do not capture OTC use and thus likely miss substantial actual use. Much of APAP use is OTC and individuals who never receive a prescription but instead obtain it from drug store shelves would not be recorded as users. Similarly, people may have started with a prescription and then switched to OTC use. These would be classified as users, but their duration of use would be misclassified and underestimated.

A particularly thorny issue in the literature on APAP and ADHD is the definition of the disease. It would seem self-evident that the “hardest” outcome is a diagnosis made by a trained healthcare professional. A nationally representative study conducted by the Centers for Disease Control and Prevention (CDC) demonstrated that about 90% of ADHD diagnoses among U.S. children were based on behavioral rating checklists and almost all (96%) included reports from parents regarding child behavior. These did not differ by age of diagnosis. In addition to parental ratings, children themselves, as well as a childcare provider or teacher were also often asked to complete checklists (about 80% in both groups). (Visser 2015) Indeed, most diagnostic guidelines require that ADHD be assessed and diagnosed by relying on information provided via a variety of methods including interviews with parents and other observers and standardized rating scales. (NIH 2018, AAP 2000, Taylor 2004)

Clinical assessments in the absence of standardized behavioral tools are problematic in their reliance on an individual expert’s subjective observations at a single point in time. High levels of variability have been shown between observing raters, in that symptoms tend to vary over time and place. (Bresslerl 2022) Moreover, clinical interviews tend to be unreliable in terms of

reproducible results from clinician to clinician. In contrast, well-established neuropsychological instruments provide standardization and, particularly for tests such as the Connor's scale, used in several of the APAP and ADHD studies, have excellent reliability. (Emser 2018) For instance, a meta-analysis evaluating the Conners Abbreviated Symptoms Questionnaire, which encompasses 5 studies with a total of 972 participants, found that it demonstrates high sensitivity (83%) and specificity (84%) in detecting ADHD. (Chang 2016) These metrics are particularly noteworthy, as high sensitivity indicates the test's ability to correctly identify patients with the condition, while high specificity refers to its accuracy in excluding those without the condition. Similarly, the Child Behavior Checklist–Attention Problems Scale, as identified in a meta-analysis involving 14 studies with 3,296 participants, shows a sensitivity of 77% and specificity of 73% in ADHD diagnosis. (Chang 2016)

All of the above suggests that a diagnosis of ADHD is not, *a priori,* more valid nor reliable than a battery of standardized assessments, particularly when those assessments are completed by more than one observer. Nonetheless, in accordance with the Court's Order of December 18, 2023, in the "Acetaminophen – ASD-ADHD Products Liability Litigation" (hereafter simply termed "The Court's Order"), my report focuses primarily on studies in which the outcome of interest was an ADHD diagnosis. As detailed below, although I considered all of the papers in this literature for context, a causal determination can (and should) be made based on the studies using diagnostic endpoints alone.

Metrics of association

Relative risks (RR: cohort studies) and odds ratios (OR: case-control studies) are measures of association, indicating how strongly *in utero* APAP exposure relates to the development of ADHD. The degree of uncertainty around the association is presented as either a p-value or a 95% confidence interval (CI).

The p-value represents the estimated probability of finding that exposure X is associated with outcome Y when in fact, the null hypothesis, that is the hypothesis that exposure X is not related to outcome Y, is true. In other words, a p-value estimates the probability of accepting a false positive association. The common terminology for p-values is statistical significance. Typically the cut-off for p values is 5% indicating that there is a 95% chance that exposure X is related to outcome Y. Statistical significance is thus the flip side of power. Power is the risk of missing a real association when one really exists, and significance is the risk of finding a spurious association when one does not really exist.

By custom, the p-value is considered statistically significant if p is quite small, often at the level of $p<0.05$. This means limiting acceptance of a false hypothesis to 1 in 20. Similarly, the 95% confidence interval represents the range of effect estimates that would be found 95 times out of 100 if the study were replicated 100 times. Any of the values within the range indicated by the confidence interval is a possible true value. Technically, the 95% confidence interval means that, when an infinite number of studies are conducted, 95% of the time the 95% confidence interval will include the true value. Smaller studies typically generate more uncertainty, i.e., broader confidence intervals. Larger studies generally produce more precise estimates denoted by tighter confidence intervals. The tighter the confidence interval, the fewer values the actual risk may be. Thus, the greater the confidence in value of the OR or RR which is at the center of the interval.

Two-sided confidence intervals that go both above and below 1.0 are considered statistically insignificant, that is, an observed association is more likely to have occurred by chance alone. For instance, for an OR of 1.3, a 95% CI of 1.0–2.0 is considered statistically significant but a 95% CI of 0.9–2.0 is considered non-significant. Risks below 1.0 represent protection such that

0.5 is a halving of risk. Risks above 1.0 are risk factors such that 2.0 is a doubling of risk. Putting this all together, an OR of 2.0 (95% confidence interval 1.3–2.7) means that exposure X likely doubles the risk of disease Y – and if the study were repeated 100 times, 95 of those times the OR would fall at or between 1.3 and 2.7, a range that since it remains above 1.0 is deemed statistically significant, i.e., unlikely to represent chance alone. Despite the report of the OR as a 2-fold increased risk, the study indicates that a risk of anywhere between 1.3 and 2.7 is possible with 95% certainty.

A large OR or RR within an individual study is not a means of determining the import of an association. Neither is it a means of excluding the impact of a positive result. Considering a study "null" or "negative" based on a confidence interval including 1.0 is an invalid use of statistics. If p does not reach $p<0.05$ or the confidence interval includes 1.0, the study is certainly not irrelevant but may simply be too small to detect a statistically significant effect. Webb (2020) calls the 95% intervals "arbitrary," as do many other eminent epidemiologists/statisticians. He notes that patterns of risk indicated by the full range of the 95% confidence interval are much more informative than a dichotomous focus on whether the CI includes or excludes 1.0. Moreover, strength of association is based on consideration of the literature as a whole; it is not based on any single study.

Hill did not mention statistical significance in his discussion of the criterion of Strength of Association. Indeed, although he emphasized that it is easier to conclude that a risk factor is associated with an outcome when the risk ratio is high—and made reference to excluding the play of chance—he also noted that, "In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is, in truth so. Relatively

few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat's urine contract Weil's disease." (Hill 1965)

Many prominent epidemiologists have strongly warned against the overreliance on statistical significance. To quote from the editors of the journal *Epidemiology*, "Of all the tools of our trade, there is probably none more subject to abuse than the P-value… From this avalanche of objections to P-values, we single out two. Statistical significance tests are subject to facile misinterpretation, even to the point of producing incorrect conclusions. Second, P-values are used to cull results in a mechanical fashion when more nuanced thinking is required." (Szklo 2001)

An even more contemporary commentary by the eminent epidemiologist/statistician Sander Greenland in *Nature* (Amrhein 2018) calls lack of statistical significance "nonsensical 'proofs of the null' and claims of non-association," making the point that: "An interval that contains the null value will often also contain non-null values of high practical importance… Specifically, we recommend that authors describe the practical implications of all values inside the interval, especially the observed effect (or point estimate) and their limits." (Amrhein 2019)

Along the same lines, "[s]ingling out one value (such as the null value) in the interval… makes no sense. The point estimate is the most compatible, and values near it are more compatible than those near the limits… Factors such as background evidence, study design, data quality and understanding of underlying mechanisms are often more important than statistical measures such as p-values or intervals." (Amrhein 2018)

Rothman, as well, weighed in on the question of statistical significance with the following comment, "It is unfortunate that a confidence interval, from which both an estimate of effect size

and its measurement precision can be drawn, is typically used merely to judge whether it contains the null value or not, thus converting it to a significance test." (Rothman 2008) Significance tests are a poor classification scheme for study results; strong effects may be incorrectly interpreted as null findings because authors fallaciously interpret lack of statistical significance to imply lack of effect, or weak effects may be incorrectly interpreted as important because they are statistically significant. Rather than be used as surrogate significance tests, confidence intervals ought to be interpreted as quantitative measures indicating magnitude of effect size and degree of precision, with little attention paid to the precise location of the boundaries of the confidence interval. This advice is backed by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, but nevertheless often overlooked even by reviewers and editors whose journals support the requirements. (Uniform Requirements for Manuscripts Submitted to Biomedical Journals 2010).

In 2016, the American Statistical Association stated, "Although hypothesis testing is still used as a method of inference, epidemiologists must also assess the validity, magnitude, and precision of observed associations rather than just the statistical significance of associations." (Wasserstein 2016)

This is not to say that statistical significance and confidence intervals should be discarded as a short-hand for determining the likelihood that a given result, repeated 100 times will generate the reported range 95 out of those 100 times. The point is two-fold. First, the most important and relevant feature of a RR is the central tendency, that is the actual RR number. The range around it is a reflection of uncertainty, which is largely determined by sample size. If the RR, i.e. the point estimate in the middle of the confidence interval range, is greater than 1.0, that is a positive association, whether statistically significant or not. Second, non-statistically significant findings are not negative findings, they are simply neutral findings. The fact of non-significance

around a positive RR suggests a study should be repeated in a larger sample. It does not imply non-importance. It does not imply absence of risk. It does not imply a negative result. As discussed in greater detail below, however, the analysis of the APAP-ADHD literature does not materially change based on one's view of statistical significance: the vast majority of the results are in fact statistically significant.

Confounding:

Confounding occurs when the exposure of interest (APAP) is more common among individuals with a second, incidental, risk/protective factor. If APAP exposure correlates with the second risk/protective factor, and that second factor is unequally distributed between children developing ADHD and unaffected children, i.e., it is a causal risk/protective factor, then that second factor is deemed a confounder. In the presence of a confounder large enough to explain the entirety of the association, an observed APAP effect could be spurious; APAP would simply then be going along for the ride.

Confounding factors, as noted, can be any known risk/protective factors. If the confounder increases risk and is not considered, then the observed association is larger than reality. If the risk factor is protective and unidentified, then the observed relationship is smaller than reality. The two confounding situations of greatest concern regarding the APAP-ADHD relationship are indication for use and genetics. Each can be difficult to fully take into account. Attempts to do so must be viewed in aggregate. Only by assessing the literature overall (see final section on Bradford Hill Analysis) can a determination be made as to the likelihood of whether confounding is more likely than causation in explaining the association between APAP and ADHD.

Confounding by indication

APAP is used for fever and pain. Fever has been shown to increase the risk of ADHD, although the data are sparse (see below). Since fever is an indication for APAP use, many have argued that fever and not APAP may be the factor underlying the observed association between APAP and ADHD. This concern, called “confounding by indication” potentially causes an observed risk that is beyond that warranted by true relationship. The important concept here, however, is that the confounding factor must be linked to BOTH the exposure and the outcome. (Rothman 2008)

Epidemiologic studies deal with confounding by developing models in which both the exposure of interest and potential confounders are considered together. This is called “adjusting” and from the model each factor can be considered independent of the others. Another approach to dealing with confounding is stratification in which only individuals with or without the confounder are considered at a given time. To eliminate age as a confounder, for instance, one might look at the relationship between APAP and ADHD among women age <20, 20-29, 30-39, >=40 separately within the study. Stratification is a powerful way to consider confounding but if the sample is divided into several groups, each group is smaller and reducing the sample size in each group may not be possible in a small study. Finally, confounding can be eliminated by excluding individuals with the confounder, that is, by including only individuals without the confounder.

Because there has been great concern that fever may confound the relationship between APAP and ADHD, let us consider the possibility of confounding by the indication of fever in more detail.

Two cohorts have assessed fever and ADHD. A meta-analysis assessed fever and neurodevelopmental outcomes overall. In this analysis, five cohort and five case-control studies

were included. However, the analyses did not break-down the data by ADHD vs. other diagnoses. (Antoun 2021)

The first cohort evaluating fever and ADHD again used data from the Danish National Birth Cohort (DNBC). Dreier et al. in 2015 and again in 2016 evaluated 89,146 pregnancies enrolled during 1996 to 2002. (Dreier 2016, Dreier 2015) The same methods were used as described above in the Atladottir study. Fever exposure was assessed by self-report during telephone interviews at gestational weeks 12 and 30. Registry information from nationwide hospital, clinic, and prescription databases was used to determine ADHD status. Fever in the late part of 1st trimester (gestational weeks 9–12) was associated with a HR of ADHD of 1.33 (95% CI 1.12–1.58). Quoting from the authors, “For the remaining part of the pregnancy fever did not seem to have any strong association with ADHD. A similar pattern was observed when the analyses were restricted to women reporting no use of antipyretic medication, suggesting that the finding was not explained by any potential harmful effects associated with acetaminophen exposure.” (Dreier 2015)

A second cohort study of fever and ADHD was conducted within the Norwegian Birth Cohort (MOBA). (Gustavson 2019) Using data collected from 1999 to 2008, the authors included more than 114,000 children in their analysis. Exposure measures were by questionnaires at pregnancy week 17, week 30, 6 months post-partum and 3 years. Information about children’s ADHD diagnoses was obtained from the Norwegian Patient Register and maternal reports of inattention and hyperactivity/impulsivity symptoms at 8 years. Maternal fever in the first trimester was associated with an ADHD diagnosis more often in exposed than unexposed children (OR 1.31, 95% CI 1.06–1.61). For children exposed twice or more in the first trimester, the OR was 2.64 (95% CI 1.36–5.14). Results were similar whether the mother had taken acetaminophen for their fever or not. No associations were apparent for registry-based ADHD

diagnosis in relation to fever in the second trimester (OR 1.13, 95% CI 0.95–1.34) or third trimester (OR 1.06, 95% CI 0.77–1.46).

Fever, thus, presents a theoretical concern of confounding by indication. However, that concern is mitigated by several lines of evidence. First, the literature suggesting that fever is associated with ADHD is far less robust than the literature linking APAP exposure to ADHD.

Second, observed effects of fever on ADHD risk were limited to its occurrence in the first and perhaps second trimesters. In contrast to the timing of risk from fever, use of APAP appears to have its greatest impact on neurodevelopment in the second and third trimesters (see for example, Chen 2019, Bauer 2020, Liew 2016, Liew 2019, Dean 2012 (rodent model sensitive window), Philippot 2017 (rodent model sensitive window))

Third, only a single cohort study (Gustavson 2019) found a risk from fever after adjustment for APAP use. Other studies did not, in general, adjust for medication use or found that the risk from fever was attenuated after adjustment for medications. This leaves unanswered the question of whether it is fever or APAP use that may be driving the fever and ADHD association, i.e., whether in fact fever is associated with ADHD in part because febrile women take APAP and APAP causes ADHD.

Concern about concomitant use of NSAIDS has also been raised as an indication-related confounding factor. Brandlistuen (2013), Havdahl (2022), and Tovo-Rodriguez (2018) all addressed this possibility using different approaches and none found evidence directly implicating NSAIDS as risk factors for ADHD.

A final potential risk factor that might result in confounding by indication is pain. Long-term APAP use (what has shown the strongest association with ADHD) is mostly used for pain and not as often for fever. Vlenterie (2016) showed that indications for >28 days use in MOBA were headache or migraine (80.2%), back pain and pelvic girdle pain (66.0% and 49.9%, respectively), and fever (24.9%). Based on acetaminophen diaries, Bandoli (2020) found that women using APAP for more than 20 days reported that they used it for headache (52%), pain or injury (27%), cold or flu (13%), and fever (only 4%). Pain is not a confounder, however, in that there is essentially no evidence that pain during pregnancy (headache, back pain, etc.) increases the risk of a child being diagnosed as ADHD.

Nonetheless, confounding by indication has been addressed extensively in the APAP-ADHD literature. Each of these studies are reviewed below and the data is then summarized regarding confounding by indication in the section on Bradford Hill Analysis: *Systematic error*.

Confounding by genetics, familial aggregation, or other unmeasured factors.

Because genetics and shared family environment (familial aggregation) are more difficult to measure, such unmeasured confounding looms large over the APAP literature. A variety of study designs can be and have been employed to try to ameliorate the potential impact of genetic confounding on the association between APAP and ADHD. These include sibling designs; negative controls (NCE); propensity scoring; and adjustment for risk factors such as genetic risk score or factors known to be associated with susceptibility to ADHD in mothers such as parental diagnosis of ADHD and other mental health conditions.

Sibling designs, conducted to limit genetic confounding, compare siblings within a given family, one exposed to APAP in utero and the other not exposed. The question is then, did the exposed child develop ADHD whereas the unexposed did not? Sibling designs limit genetic effects as

well as shared familial exposures. However, they do not exclude genetic nor familial aggregation. Most siblings share only 50% of their genes. Moreover, it is quite possible that mothers of children who have developed symptoms of ADHD might avoid taking any medications, including analgesics in the next pregnancy and may change other pregnancy and post-natal behaviors to limit any possible adverse exposures. Thus, siblings would not share pertinent environmental factors. Finally, epigenetic effects not shared by siblings (genetic alterations that do not relate to the genetic code of the mother or father but occur after conception) might be an important aspect of the genetics of ADHD. This is a likely explanation for the fact that first births are more likely to be affected by ADHD than subsequent births. (Reimelt 2021, Carballo 2013, Martin 2014) Use of siblings as controls would not overcome this issue. Thus, sibling studies limit but do not exclude shared familial confounding.

Propensity matching is a sophisticated statistical design that attempts to limit confounding by matching a selected group of controls to cases within a cohort. The propensity score allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the attributes of a randomized controlled trial. In particular, the propensity score is a balancing score: conditional on the propensity score, the distribution of observed baseline covariates will be similar between treated and untreated subjects. The system relies on collected covariates with the idea that by balancing these, it also balances unmeasured characteristics.

The use of negative control exposure (NCE) is a clever way to assess an exposure-outcome relationship using a counterfactual. NCE uses variable(s) that do not causally affect the outcome but share a similar confounding structure with the exposure variable of interest. However, a NCE for genetics should be a counterfactual. That is, it should reflect something about the underlying genetics of the mother. Studies that measured APAP use before and/or after pregnancy in comparison to use during pregnancy are useful NCEs representing exposure

effects during vs. not during the period of relevant sensitivity. However, paternal behavior is questionable as a useful NCE in that it is difficult to understand how this reflects underlying maternal genetics.

Genetic risk scores for ADHD use an aggregate of previously discovered allelic variants. These studies hypothesize that because a confounding factor must relate to both exposure and outcome, demonstration of a link between genetic score to APAP use suggests the potential for genetic confounding. Once the ADHD risk score is associated to APAP use, it must be tested as a potential confounder by controlling it in an analysis of prenatal APAP exposure and ADHD outcome. That is, a genetic risk score moves from being a hypothetical confounder to a demonstrated confounder only when shown to eliminate the association in a cohort or case-control study of prenatal APAP use and ADHD risk.

A final method for addressing genetic confounding is adjustment for parental ADHD or related mental health diseases. This would reduce the potential for genetic confounding as well as possibly familial aggregation.

Below I will consider each of these methods as applied to the APAP-ADHD literature. Specific results are shown for each study and then the totality of approaches to address genetic confounding is considered in the section Bradford Hill Analysis.

Other potential sources of confounding

In past studies, the most concerning confounding factors have related to general health and health-seeking behaviors. For example, individuals who take vitamins and supplements tend to have a variety of other healthy behaviors that diminish their risk for a variety of diseases. Because healthy behaviors are positively associated with the exposure and negatively

associated with the outcomes, their effect has been to inflate the size of observed protective effects. Whereas observational studies suggested that supplements reduced the risk from heart disease, randomized clinical trials failed to demonstrate benefits. That is, in the case of vitamin/mineral supplements, a consistent reduction in risk was shown in cohort studies but not confirmed upon administering those vitamin/mineral supplements to participants.

A major reason why healthy behavior was a persistent confounder is that individuals participating in research tend to be more likely to be healthy. Moreover, they engaged in complex dietary and exercise behaviors known to reduce risk of heart disease. Thus, adjustment was an inadequate means for eliminating confounding effects.

This analogy breaks down in the case of APAP and ADHD wherein the situation is quite different. First, as shown by Bandoli (2020), almost 2/3 of women take APAP during pregnancy, i.e., are ever users. Not all of them could have the same set of health behaviors. Thus, a consistent finding that ever use of APAP increased risk of ADHD is unlikely to have spuriously resulted from overall health differences between users and non-users.

The analogy is not apt even in the case of longer-duration users who Bandoli showed are less healthy, i.e., are more likely to use tobacco, have obesity, self-reported depression or anxiety, and antidepressant use. Thus, these are potential confounding factors, although all have been considered and adjusted for in various analyses (see below). Yet, women who are healthy are often more likely to engage in research so study participants likely underrepresented unhealthy women – those with the confounder. (In the above example of vitamins and heart disease, study participants overrepresented individuals with the confounder.) In two of the largest and most dominant studies in the literature (MOBA and DNBC) wherein drop-out and missing data rates were high, over-representation of healthy women likely led to deflation of observed effects.

Bias.

In epidemiology, bias represents any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and the health outcome. Bias occurs when an estimated association such as an odds ratio deviates from the true measure of association. Bias can either be towards the null, i.e., underestimate the true risk, or away from the null, i.e., overestimate the true risk. The source of bias of greatest concern in the APAP and ADHD literature is selection bias. If women enrolled in studies, particularly those using APAP, had other characteristics that made them less likely to have children with ADHD, this would result in an underestimate of the true effect.

The two largest cohorts that have contributed data to the literature on APAP use and neurodevelopment, DNBC and MOBA both potentially suffer from bias resulting from differences between women participating and continuing to participate versus those not. DNBC enrolled only 31% of eligible women into the cohort. MOBA had a 40% response rate. Nilsen et al. (2009) evaluated the differences between those who agreed to participate in MOBA compared to all women in the national Norwegian population-based birth registry. (Nilsen 2009) The authors found a strong under-representation of the youngest women (<25 years), smokers, and women with stillbirths and neonatal death in MOBA, while multivitamin and folic acid supplement users were over-represented. It is not clear that selection bias in enrollment would impact exposure-outcome relationships. However, MOBA also experienced high drop-out rates (40%), which almost surely would impact risk estimates. It is likely that women willing to remain in the study had similarly biased demographic characteristics to those willing to participate. These data, then, suggest that women in the cohort were older, without previous adverse birth outcomes, non-smokers, with better health behaviors—factors that would have made them less likely to have a child with ADHD.

As a result of selection bias, results from MOBA likely underrepresent true risks of APAP in relation to ADHD. Similarly, in the DNBC about 30% of the eligible mothers missed one or more telephone interviews, which eliminated them from analyses. As noted by de Fays (2015) on behalf of the European Medicines Agency, DNBC may "underrepresent ADHD because it is thought to be largely heritable, and dropout may be different depending on the ADHD status of the parents." Again, the selection bias would result in bias toward the null.

Exposure misclassification:

While cohort studies ensure that the exposure preceded the disease and that the presence of disease does not influence recall of exposure, they do not exclude faulty recall. In many of the cohort studies, women were queried during the pregnancy and thus their memories for exposures were fresh and reliable. Others asked about the pregnancy experience at or after the birth of the infant. These would have relied on longer-term memory. Since the prenatal period is one in which women scrutinize their exposures more than any other time in life, this may not be a large issue, but it does warrant some additional caution in interpreting such studies.

Most studies were not designed specifically to look at APAP use and so did not ask the specific question, "did you use acetaminophen, when and how often?" Instead, they asked about the use of medications in general or analgesics in general, or medications for specific indications. This allowed for reporting of a wide array of medications and then analysis of APAP independent of other medications. However, women who did not consider OTC APAP use to be a medication likely did not report use, leading to underestimation. As per the DNBC referenced above, only one quarter of women mentioned analgesic use on untargeted questionnaires about use of any medications, whereas over half reported analgesic use on targeted queries. Studies

using checklists in which analgesics were specifically queried by name would have resulted in a more complete exposure profile than open-ended questionnaires, but in the literature overall, there is almost certainly a systematic underreporting by both women whose children were bound to develop ADHD and among those whose children were not. This would have resulted in non-differential misclassification and a bias toward the null, i.e., an undervaluation of the risk.

Exposures categorized as ever/never almost surely underestimate true risk. Such studies aggregate pregnant women with long duration and/or high dose use of APAP with women only minimally exposed to APAP. It is easy to see why such categorization would underestimate any true risk.

A limited number of studies have assessed longer duration use (typically >28 days) or in multiple trimesters. None assessed a quantitative measure of dose in milligram terms, which requires knowing the amount as well as the duration of use. Lack of data on amount of use, even in these long-duration analyses, would tend to bias results toward the null because such analyses would admix users of high and low frequency. (Rothman 2008) That is because, for instance, women using APAP several times a day would have been admixed with those using it only once a day. Moreover, without data on dose, women using an extra strength APAP would have been admixed with those using regular dosage APAP. In both situations, the actual quantitative dose in milligrams (calculated as dose x duration) was unknown. In both situations, the impact from high dose/heavy use was diluted by lighter use. Women exposed for longer duration and for more trimesters have been found to be at greater risk of having an affected offspring. Yet, still, this likely underestimates the risk of true high dose users.

Other “hard” exposure ascertainment methods may have resulted in similar or even worse misclassification. Pharmacy records underreport APAP exposure since they typically do not

capture OTC sales. Cord and serum blood measured APAP concentrations only when exposure occurred within the preceding 48 hours or so. If the biologic specimen was obtained at delivery and hospital protocol was to administer APAP during labor, the relationship to earlier patterns of APAP use would have been null and void. These considerations would uniformly have led to misclassification toward the null since outcome was unknown at the time of APAP exposure assessment. Of all the measures used, fetal meconium, which concentrated APAP use over the final two thirds of the pregnancy, is the most accurate metric for assessing both use and dose. (Baker 2020, Ostrea 2006, Delano 2019, Lange 2014)

For the outcome of ADHD, misclassification was also ubiquitous. Maternal/teacher reports of behaviors were subjective and subject to bias, sometimes linked to maternal characteristics that related to susceptibility to ADHD. For instance, women with depression/anxiety may have been more or less sensitive to their children's behaviors. Teacher reports are also subject to misclassification since children behave differently in classroom and home settings.

Correlation between reporters lends credibility to self-reported measurements. Inoue (2021) showed a high correlation between child reports of behavior and maternal assessments. Brandlistuen (2013) demonstrated that maternal reports correlated significantly with urine measurements of APAP. Finally, Ruisch (2008) found that results from teacher and parental reports correlated. These findings are reassuring. Nonetheless, for all the reasons cited above, bias toward underestimation of risk almost surely accompanied self-reported data.

Registries only collect data on children that seek medical attention and thus, presumably have more severe disease. Psychiatric diagnoses are available only when more impacted individuals seek such care. All these measures of outcome, then, are subject to large degrees of

misclassification, almost all of which would have resulted in non-differential misclassification. The error would have underestimating risks.

Language of professional epidemiology

The standards of epidemiologic discourse in published papers are extraordinarily conservative when it comes to use of causation language. Scientists are trained to be conservative, even humble, in their claims. As per the Reference Manual, "Generally, researchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn." (Reference Manual on Scientific Evidence, p 599) Discussion sections, by definition, include the longest list of limitations an author can conjure. Almost all epidemiologic studies end with the caveat, "more studies are needed…" or some variant thereof. This statement demonstrates that the author is not overreaching in their interpretation or claims of their particular study.

It is the exceedingly rare article that asserts that an association is causal. Even the Women's Health Initiative, the massive randomized clinical trial that established a definitive link between use of post-menopausal hormone therapy (HT) and breast cancer made a public health recommendation but did not assert causality. (Rossouw 2002) Yet, this study led to striking reductions in the worldwide use of HT and a subsequent fall in the incidence of breast cancer. Indeed, the standard in the field is to claim causality only after an exhaustive systematic review within the framework of Hill's tenets.

Authors will suggest major public health action before they deem a risk factor to be definitively causal. This seems counterintuitive but the professional framework for this seemingly backwards approach is the precautionary principle of "first do no harm." That is, even in the absence of a full assessment of whether the association meets Bradford Hill's criteria,

professionals will recommend that a potential hazard be removed from the marketplace or the environment to limit potential harm, if they consider the good of doing so exceeds the risk of not doing so.

In the case of APAP use during pregnancy, Bauer et al. (2021) advocated for cautionary medical advice and product labeling. Specifically, the authors suggested that pregnant women, "forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long-term basis; and minimize exposure by using the lowest effective dose for the shortest possible time." (Bauer 2021)

Moreover individual authors couched their findings in professionally appropriate moderating language. These were presented under the heading "Limitations" since authors are bound to come up with any and every possible caveat in this mandatory section of publications. Thus, Liew (2014) wrote: "Nevertheless, the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or coexposures to other medications cannot be dismissed." Ystrom (2017) cautioned: "However, given that paternal use of acetaminophen is also associated with ADHD, the causal role of acetaminophen in the etiology of ADHD can be questioned. We do not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD." Ji (2018) said, "third, although we adjusted for major known risk factors of ADHD and indication of acetaminophen use, we could not adjust for several familial factors identified in previous studies. We also cannot rule out the possibility of unmeasured or unknown residual confounding, although our propensity score analyses seek to adjust for such confounding and provide additional credibility for our findings." Liew (2019) indicated, "future investigations are still needed, especially studies with improved exposure and outcome assessment and studies with the ability to address known and possibly unknown confounding factors in the analyses." Ji (2020) added, "because of our observational

study design, we were unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors." Baker (2020) said, "Confounding by unmeasured or unknown factors is always a possibility . . . lack of confounding by indicators in prior cohort studies does not necessarily apply to the cohort studied herein." Ricci (2023) noted: "However, the certainty of the evidence on this topic is low, and findings should be interpreted in light of the limitations of the existing studies, as well as the limited number of sufficiently comparable studies available to meta-analyses."

Again, such cautionary language simply shows that the authors are not making overly ambitious claims about their particular study results and are aware of all the concerns addressed below in my analysis. Moreover, since none of them embarked on a complete Bradford Hill assessment—or review of the entirety of the literature up to the present day, as I have done—none made claims for or against causality, as is professionally appropriate.

Professional societies, which are often slow in limiting physician's prescribing flexibility, have seemingly disagreed. Presumably, they are protecting the use of APAP as the only drug currently considered a safe and effective medication to treat short-term fever and minor pain during pregnancy. However, these organizations have done so without engaging in their own systematic reviews. European and Canadian professional societies (European Network of Teratologic Information Services or ENTIS and Society for Gynecology Canada or SOGC) both questioned the case for causality, citing "weak evidence." However, this was not a refutation of the call for precautionary action. It was, instead, a questioning of causality in the absence of their own complete review of the data. In contrast, the only American professional society to weigh in was ACOG. In response to the consensus statement in 2021, ACOG stated, "[t]his consensus statement, and studies that have been conducted in the past, show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during

any trimester and fetal developmental issues." (*ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy*, Sept. 29, 2021) Note the language, "prudent use." In other words, although seemingly opposing the consensus statement, ACOG actually agreed in a key respect that prudence should be employed in the use of prenatal APAP.

APAP indication, use, and perception

Indications for APAP use include short-term fever, minor aches, and pain. It is not indicated for long-term, severe pain or for long-duration fever. From the J&J Tylenol website:

"Acetaminophen is most commonly used to treat minor aches and pains, including headache, backache, minor pain of arthritis, toothache, muscular aches, premenstrual and menstrual cramps. It is also commonly used to temporarily reduce fever." (J&J 2023) (my underline added)

Severe pain often necessitates pharmacologic intervention, but APAP is indicated for minor pain, which may be treatable using non-pharmacologic modalities. Long-duration fever requires clinical assessment, a causal explanation, and targeted treatment that goes beyond symptom control.

Longer-term APAP use is mostly for treating pain and not as often for fever. Vlenterie (2016) showed that indications for >28 days use in MOBA were headache or migraine (80.2%), back pain and pelvic girdle pain (66.0% and 49.9%, respectively), and fever (24.9%). Based on acetaminophen diaries, Bandoli (2020) found that women using APAP for more than 20 days reported that they used it for headache (52%), pain or injury (27%), cold or flu (13%) and fever (only 4%).

Thus, the indication for only one quarter or less of APAP use is fever or cold/flu. Pain, the more common indication, is not a confounder in that there is essentially no evidence that pain during pregnancy (headache, back pain, etc.) increases the risk of a child being diagnosed as ADHD.

Many studies adjusted for pain or infection or both and found no evidence that it confounded the relationship between APAP use and ADHD. (Brandlistuen 2013, Liew 2016, Masarwa 2020, Inoue 2021 (see below))

A few comments on APAP relative to my assessment

Prenatal APAP safety assessment.

The current guidance from ACOG regarding APAP during pregnancy is, “ACOG and obstetrician-gynecologists across the country have always identified acetaminophen as one of the only safe pain relievers for pregnant individuals during pregnancy.” (ACOG 2021)

The validity of the claim that APAP use during pregnancy is safe has recently been assessed in a comprehensive literature review by Cendejas-Hernandez (2022). Of 3000 articles considered by the authors, 218 made claims that paracetamol (APAP) use in infants or children is safe. Approximately half provided no citation. The other half often cited “primary” articles which did not make original claims of safety, but rather cited additional (“secondary”) articles. Only 52 studies provided experimental evidence supporting claims of safety. Median follow-up time was just 48 hours. Six studies had follow-up times of longer than 10 days, although only one study evaluated patients beyond 6 weeks and in this study, the only endpoint was hospitalization. No study assessed neuropsychiatric function.

Cendejas-Hernandez et al. (2022) concluded, “assertions that paracetamol is safe during early development when used as recommended are based on a lack of knowledge regarding the effects of paracetamol on neurodevelopment.” Thus, ACOG’s statement regarding the safety of APAP appears to be based on *not recommending anything counter to what is already done by obstetrician-gynecologists,* rather than on research. In turn, because physicians are counseled

by ACOG and the pharmaceutical industry that APAP is safe, the statement "[c]onsult with your physician" is sure to reinforce reassurance. However, that reassurance is not evidence-based.

Rather than relying on a rigorous assessment of safety, the use of APAP dominantly grew out of a concern in the early 1980s that aspirin was associated with Reye's syndrome in children with viral illness, making APAP the antipyretic and analgesic of choice for children and for pregnant women. Moreover, convincing evidence about a link between NSAIDS and congenital malformations, prenatal ductus arteriosus constriction, oligohydramnios, neonatal renal failure, and primary pulmonary hypertension, began mounting in the early 2000s. (Stika 2002, Sawdy 2003, Groom 2005) In 2020, the FDA issued a warning that NSAIDS should not be used in the second and third trimesters of pregnancy, making APAP the only analgesic that did not appear, at that point, to have *in utero* toxicity. (FDA 2020) APAP thus became the only antipyretic/analgesic recommended for pregnancy use beyond the first trimester.

Acetaminophen has a surprisingly narrow therapeutic window. Although it has an excellent safety profile when taken in doses representing the bottom or middle of its therapeutic range, when taken at the top of the recommended range, it can induce serious, even fatal, hepatotoxicity. Toxicity results from the depletion of endogenous glutathione and subsequent shunting of paracetamol metabolism from the usual benign excretion pathway to a toxic inflammation-inducing pathway, as reviewed below under Bradford Hill Analysis: Biologic plausibility. (Carreia 2007)

It is easy to overmedicate with APAP, triggering toxic metabolism. The recommended dose of Extra Strength Tylenol (500 mg) is 1 to 2 tablets every 4 to 6 hours. Someone in severe pain might reasonably take 2 tabs every 4 hours or a total of 12 tablets in a 24-hour period. Their day's dosage would thus be 6000 mg. However, more than 4000 mg represents a dangerously

high dose. According to the Harvard website, “The maximum daily dose for a healthy adult who weighs at least 150 pounds is 4,000 milligrams (mg). However, in some people, taking the maximum daily dose for extended periods can seriously damage the liver. It's best to take the lowest dose necessary and stay closer to 3,000 mg per day as your maximum dose.” (Harvard Health, *Acetaminophen safety: Be cautious but not afraid* 2020) A similar warning has been issued by FDA: “severe liver damage may occur if you take more than 4000 mg of acetaminophen in 24 hours.” (FDA 2015) “Intake of more than 4000 mg should prompt medical assessment and therapeutic intervention to salvage a damaged and/or failing liver,” according to reviews of the topic. (Yoon 2016)

Summary

APAP has been used for many decades. It has grown in popularity to occupy a major place in the analgesic and antipyretic armamentarium, particularly during pregnancy. ACOG and obstetricians in general consider it safe and effective, and it is the primary drug recommended for use among pregnant women. Women often do not consider APAP to be a medication and underreport its use. However, the assumption that APAP is safe has not been adequately studied. At higher dosages, APAP is known to be unsafe - causing hepatic toxicity that can lead to liver failure and death. ACOG recommends “prudent use,” as did the Bauer et al. (2021) consensus statement which urged caution and for women to “forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long-term basis; and minimize exposure by using the lowest effective dose for the shortest possible time.”

Systematic review of studies on APAP and ADHD that I included in my Bradford Hill analysis

I have considered in my Bradford Hill assessment of causality only studies that used ADHD diagnosis as endpoint, in keeping with the Court's Order indicating that, "If the studies for . . . ADHD were subjected to their own individual Bradford Hill analysis, it would be easier to discern whether there was actual support for a finding that prenatal exposure to acetaminophen causes . . . ADHD." (Order at 63)

Studies using reported behavioral assessments as endpoints are included after my review of the primary studies contributing to Bradford Hill as context, not as part of the primary analysis. It is entirely possible (and correct) to make a causal inference based only on the set of studies that have looked at ADHD diagnoses.

Summary of individual studies

Liew (2014)

Using data from the Danish National Birth Cohort (DNBC), Liew (2014) assessed the relationship between APAP use during pregnancy and ADHD medication prescriptions or hyperkinetic disorders in children. DNBC is a large, population-based cohort with long-term follow-up.

DNBC enrolled pregnant women during the period 1996 to 2002 and has followed them ever since. Women were recruited between 6 and 12 weeks of gestation by approximately 50% of all general practitioners in Denmark. Sixty percent of women invited agreed to participate.

The DNBC enrolled 101,041 pregnant women from the general population of Denmark. Of these, 64,322 had live-born children and information from telephone interviews conducted at 12 and 30 weeks of pregnancy and at 6 months post-partum, as well as a self-administered

online/mail questionnaire when children had turned 7 years of age. Thirty-one percent of subjects have missing data at one or more telephone follow-up.

Exposure assessment of analgesics was queried with the question, “did you take pain killers?” If yes, the respondent chose from a list of 44 medications, including APAP. Analgesic use was asked for each week of pregnancy so that both timing and duration could be calculated.

In addition to follow-up interviews, outcomes were ascertained using population-based registry data. Denmark has a system of national health insurance in which almost all citizens participate. Linking these data to interview data results in a limited amount of missing data and limited selective misclassification. The outcome of hyperkinetic disorder was categorized if diagnosed according to the national general hospital registry as well as the psychiatric hospital registry. Since 1995, both inpatient and outpatient data are included in these registries. ADHD medication use (Ritalin, atomoxetine, or modafinil) was garnered from the Danish Prescription Registry, which, since 1995, receives data on dispensed prescriptions from all pharmacies in Denmark. ADHD-associated behavioral problems were ascertained using the Strengths and Differences Questionnaire (SDQ).

Many confounding factors were included in the analyses, including maternal age, parity, socioeconomic status, smoking, alcohol use, BMI, psychiatric illnesses, diagnosed anxiety/depression, maternal childhood psychiatric disorder, maternal family problems/life crisis, and maternal childhood behavior problems. Indications for analgesic use such as fever, inflammation/infection, and diseases of muscles/joints were queried, as were use of aspirin and non-steroidal medications, folic acid, antibiotics, sleep medicines, and anti-depressants. Children’s sex and year of birth were adjusted in models. Other potential confounders

considered were father's age at the child's birth, Apgar scores, and season of conception. Only 5% of subjects had missing covariates.

Follow-up to the time of the Liew publication was an average of 12.7 years. The mean age of children at the end of follow-up for hyperkinetic diagnoses was 10.7 years and for ADHD medications was 11.2 years.

More than half of all mothers reported APAP use while pregnant. The authors observed an increased risk for ADHD-like behaviors in children at age 7 years after maternal APAP use during pregnancy. Children whose mothers used APAP during pregnancy were at higher risk for receiving a hospital diagnosis of hyperkinetic disorder (HR 1.37; 95% CI, 1.19–1.59) and of use of ADHD medications (HR 1.29; 95% CI, 1.15–1.44). (Liew 2014, tbl 4)

Risk increased for use in more than one pregnancy trimester, especially in later pregnancy. Significant trends were found with increasing duration for hyperkinetic diagnosis and ADHD medication use. (see Liew 2014, tbl 4)

Moreover, for both ADHD medications and hyperkinetic diagnosis, use in all three trimesters imparted the greatest risk and was statistically significant. For hyperkinetic disorders, the adjusted RR was 1.61 (1.30–2.01); p trend <0.001 for ADHD medication use, it was 1.44 (1.21–1.72); p trend <0.001.

Use of APAP in the third trimester increased ADHD medication risk significantly (RR 1.28, 95% CI 1.08–1.52) and hyperkinetic diagnosis to about the same degree (RR 1.22, 95% CI 0.97–1.53) (albeit non-significantly). Second and third trimester use increased risk more than use in the first for ADHD medications but not hyperkinetic disorder diagnosis. Some of these subset

findings were not statistically significant as would be expected based on smaller sample sizes. As the Court's Order noted, the associations "for second or third trimester use, for use in both the first and second trimesters, or for use in both the second and third trimesters" were not statistically significant for HKD diagnosis. (Order at 28) For these results, however, lack of statistical significance does not imply a negative finding, simply a null finding, especially when the point estimate was positive and similar to the statistically significant results in magnitude. Adjusted first vs. second/third trimester RRs for ADHD medications were: 1.09 vs. 1.28. This demonstrated that for both endpoints, more trimesters of use translated to greater risk, and that for ADHD medication use, the later in pregnancy the more sensitive the fetus seemed to be to APAP exposure.

Similarly, risk from APAP use among women reporting longer-duration use was greater than among women with shorter duration exposure. APAP use during pregnancy for 1 week, 2.5 weeks, 6-10 weeks, 11-20 weeks, and >20 weeks, as compared to no use, yielded adjusted RRs for ADHD medication of 1.27, 1.43, 1.74, 1.49 and 1.78 (test of trend $p<0.001$). Use of APAP for 20 or more weeks during pregnancy also elevated a child's risk for receiving a hyperkinetic diagnosis by almost 2-fold (adjusted HR 1.84, 95% CI 1.39–2.45) (test for trend $p<0.001$). None of the confounding factors evaluated, including maternal inflammation, infection during pregnancy, mental health problems, or other potential confounders, negated these observed associations.

Notably, not all estimates were significant in the interpretation of these dose-response data. However, as noted above, significance is not the equivalent of meaningful. By parsing the data into many categories, power was lost, and it is not surprising that estimates were not always significant. What is important is the clear pattern that estimates increased with duration of use.

Liew Critique

According to Liew (2014): “Using prospective data from a well-designed large cohort of pregnant women with a long duration of follow-up and registry based outcome assessment, we found that prenatal exposures to acetaminophen may increase the risk in children of receiving a hospital diagnosis of HKD or ADHD medication with greater frequency of use increasing risk in an exposure-response manner.”

Liew et al.’s interpretations with respect to confounding were: “Results did not appear to be confounded by maternal inflammation and infection during pregnancy, mother’s mental health problems, or any of the other fac-tors we evaluated.” (Liew 2014) “We adjusted for several indications that might have triggered maternal acetaminophen use in analyses, and results also did not differ for women who did and did not report infections/ inflammations during pregnancy or when controlling for use of common nonsteroidal anti-inflammatory drugs.” (Liew 2014)

The Liew (2014) authors also wrote about their findings with respect to dose response as follows: “The associations were stronger for acetaminophen use in more than 1 trimester, and we found exposure response trends with increasing frequency of use during gestation.”

The study was large, allowing for excellent precision around estimates. As a cohort study, it ensured that exposure, which was captured more than once during pregnancy, would have preceded outcomes. The cohort was population-based, although response rates were not high (60%), meaning that selection bias and selective misclassification of exposure likely occurred. However, because two of three outcome measures were from registry data, the selection bias from missing telephone interview data for these was limited.

Potential confounding was limited by inclusion of many covariates in mothers, fathers, and offspring. Confounding by indication was well adjusted by including in models both indicators of fever and pain. Consideration of genetic confounding included multivariable model control for psychiatric illnesses, diagnosed anxiety/depression, maternal childhood psychiatric disorder, maternal family problems/life crisis, and maternal childhood behavior problems. These variables would have limited both genetic and familial aggregation effects.

National hospital and pharmacy registries promoted the validity and reliability of data. Moreover, ascertainment of exposure data at each of the second and third trimesters allowed for assessment of intra-reporter consistency and of duration of use. Follow-up was long enough to capture many of the signs and symptoms associated with ADHD, since that diagnosis is typically made by the pre-teen years.

Exposure misclassification of APAP use was limited by use of a checklist of analgesics by name and by ascertainment of analgesic information at three time points during and shortly after pregnancy.

Weaknesses included that, to be captured by the registry for ADHD medication use, cases might have had more severe forms of illness, triggering them to seek medical attention and treatment. Similarly for hyperkinetic disorder, it may have been only the more severe cases that would have come to medical attention. However, both of these study aspects could be considered strengths (not weaknesses) since more severe cases would be less likely to be misdiagnosed.

Unadjusted confounding must be considered in any epidemiologic study, no matter how excellent the design. In particular, limited adjustment was conducted around children's

characteristics at birth (e.g., birthweight) and during childhood (e.g., other medication use). Unmeasured genetic confounding may have also occurred. As the authors noted, although they did "adjust for several indications," "the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or coexposures to other medications cannot be dismissed."

Overall, Liew (2014) was a study of high quality and showed effect sizes on the order of 40-60% for ever/never APAP use and ADHD medications or hyperkinetic diagnosis, and risks elevated about 80% among long-duration users. The fact that longer duration users demonstrated higher risks argues for a dose-response. Moreover, the study identified later pregnancy use as a sensitive window with risks of ADHD medications and hyperkinetic disorders.

Ystrom (2017)

In a secondary data analysis of the Norwegian Mother, Father and Child Cohort Study (MOBA), Ystrom (2017) addressed use of prenatal APAP and resultant children receiving ADHD medications or a clinical hyperkinetic disorder diagnosis. MOBA is unique in its size, length of follow-up, and inclusiveness of data collection. Over 90,000 pregnant women were recruited from 1998 to 2008. More than 70,000 fathers participated. Data were collected at baseline and in every trimester of pregnancy, as well as at birth and every two years or so among parents and children. Follow-up is ongoing. Outcomes and potential confounders were ascertained using data from comprehensive population-based registries. The availability of such data, linked to collected data, resulted in a limited amount of missing data and a limitation in selective misclassification.

The Ystrom (2017) authors used data from 1999 to 2008, involving 48,631 child-mother pairs who had completed a questionnaire when the child was age 3. Follow-up of the cohort involved

questionnaires at pregnancy week 17, 30, 6 months post-partum, and at 1.5 and 3 years. Follow-up was only until 3 years of age. An almost 50% rate of loss-to-follow-up is an issue for MOBA. Thus, diagnoses in this analysis were highly reliant on registry data.

APAP exposure was queried in any woman reporting headache, fever, cold, or backache. Among such women, medication use was asked in an open-text format. Timing and duration were also ascertained.

This analysis was based on a final sample of 112,973 children and their parents (this larger number reported by the Ystrom (2017) authors includes the number of children plus mothers and fathers participating).

The outcomes of children's ADHD diagnoses were obtained from the Norwegian Patient Registry. Since 2008, all government-owned and government-financed hospitals and outpatient clinics are mandated to report individual-level, International Classification of Diseases, 10th Revision (ICD 10), diagnoses to the Registry to receive reimbursement. The ICD 10 codes used were for ADHD overall and also for hyperkinetic disorder. Hyperkinetic disorder requires the combination of inattentive and hyperactive symptoms, and is a subtype nested within the DSM classification of ADHD. Patients with hyperkinetic disorder, according to the Ystrom (2017) authors, suffer from more language and motor development problems than among children with ADHD overall.

Children with ADHD, as compared to those without the diagnosis, were more likely to be exposed in utero to APAP during the second trimester (39% vs. 35%) and third trimester (71% vs. 67%). After adjustment for potential confounders, risk elevation for ADHD among APAP use was (HR 1.12, 95% CI 1.02–1.24) for any use during pregnancy, in one trimester was (HR 1.07,

95% CI 0.96–1.19), in two trimesters was (HR 1.22, 95% CI 1.07–1.38), and in all 3 trimesters (HR 1.27, 95%CI 0.99–1.63). The HR for more than 29 days of maternal APAP use was 2.20 (95%CI 1.50–3.24). In contrast, use for <8 days was negatively associated with ADHD (HR 0.90; 95% CI 0.81–1.00). This may suggest that taking an anti-pyretic for a short period for fever may reduce ADHD risk. This, however, does not detract from the result that long-term use increased risk, since the indications for long-term use are typically not fever, as discussed above.

Although the relationship between APAP use and outcomes was unaffected by adjustment for fever, acetaminophen use for fever and infections for 22 to 28 days was associated with a particularly high risk of ADHD (HR 6.15, 95% I 1.71–22.05), suggesting a potential interaction. This implies that women who take APAP long-term for fever are at substantially elevated risk for ADHD. Long-term APAP use is not recommended for fever, so both because such use is not part of the indications recommended by manufacturers and because it may greatly elevate risk for ADHD, such use may be inappropriate.

Use of APAP in two or in three trimesters, as well as use for long duration, were all statistically significant. However, as noted above, significance is not the equivalent of meaningful. Thus, my judgment is based more on the point estimates than significance, and in this analysis, long duration use increased risk by more than 2-fold. Moreover, like in the Liew (2014) study, there is an impression that more trimesters of use increased risk more than fewer trimesters.

With regard to NCE analyses, preconceptual APAP use was not associated with ADHD. However, paternal use and maternal use of APAP were similarly associated with ADHD.

Prenatal use of APAP for 29 or more days was associated with a substantially increased hazard rate of ADHD (HR 2.20; 95% CI 1.50–3.24), even after stratifying within groups by indication for APAP use. The associations with use of 29 days or more did not differ across groups of indications, such as fever and infection (HR = 2.13–2.56).

Ystrom Critique

The Ystrom (2017) authors' own interpretation of their work was as follows: "Long-term maternal use of acetaminophen during pregnancy was substantially associated with ADHD even after adjusting for indications of use, familial risk of ADHD, and other potential confounders." They go on to discuss the consideration of confounding by indication. "We had the advantage of having medication data separately for each indication, allowing us to account for confounding by each indication in a stratified model." (Ystrom 2017) "Even after adjusting for indications of use, there was still an association (HR = 2.20; 95% CI 1.50–3.24) between long-term prenatal acetaminophen exposure and childhood ADHD. This estimate was similar across several indications for acetaminophen use (fever, infections, and pain conditions). This indicates that putative confounding factors for long-term acetaminophen use and ADHD are not related to the recorded indications but are related to unmeasured factors." (Ystrom 2017)

In discussing confounding by genetics, the Ystrom (2017) authors opine: "In our study, the association persisted after adjusting for acetaminophen use before pregnancy and for parental symptoms of ADHD."(Ystrom 2017) "With our analyses, we showed that the association between maternal acetaminophen use and ADHD did not appear to be strongly confounded by common familial (eg, genetic) factors for ADHD and use of acetaminophen." (Ystrom 2017) "Maternal preconceptional use was not associated with ADHD. This is in line with a recent study in which researchers found no effect of maternal postnatal acetaminophen use on maternal reports of behavior problems. Furthermore, we found that maternal preconceptional use was as

associated with use during the first trimester as use across 2 trimesters. This supports the employment of maternal preconceptional use as a negative (or specificity) control and is consistent with a causal link." (Ystrom 2017) They then note that, "However, given that paternal use of acetaminophen is also associated with ADHD, the causal role of acetaminophen in the etiology of ADHD can be questioned. We do not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD." (Ystrom 2017)

About dose response, the Yystrom (2017) authors noted: "For use >7 days, the HR for offspring ADHD increased with the number of days exposed."

My assessment is this: Strengths of the Ystrom (2017) study are its large sample size, population sample, longitudinal design, multiple potential confounders in adjusted models, and use of comprehensive registries to capture outcome data.

In addition to these strengths, Ystrom (2017) examined both frequency of use by trimester and duration of use (>28 days or less). Risks among short duration use were reduced below 1.0, whereas longer duration increased risk, i.e., a relatively linear risk curve started below 1.0. The Ystrom (2017) authors also adjusted for indication and found it did not affect their estimates. Fever and APAP use interacted such that use of APAP among women with fever or infections imparted a particularly high risk (>6-fold).

Weaknesses inherent in MOBA analyses are high drop-out rates. Long-term APAP users were somewhat more likely to drop out (4.2% vs 3.7%). Although quite similar to non-dropouts, women who remained in the study had slightly lower depression rates and were less often "not married or cohabiting." (Ystrom 2017) As discussed above, bias in this situation would have been to underestimate the true effect size. Women using long-term APAP had healthier

behaviors, and they would have tended to have less ADHD. Because the study outcomes came from linked registry data, this placed the weight of outcome classification on registries.

Another weakness of the MOBA analyses was the short duration of follow-up for the diagnosis of ADHD and the reliance on registries. Registries likely represented only children with more severe problems. Many children with ADHD have more modest symptoms and would not come to medical attention. Moreover, children manifesting serious symptoms at a young age likely would have been those with more severe manifestations. As noted above, these may actually have been strengths in identifying a group less likely to be mis-diagnosed and thus misclassified. Other factors that limit this problem are that, first, Norwegian hospital registries also include outpatient clinic information. Second, national health insurance would have ensured access to these resources for the entire population. Third, inclusion of more severe cases would have, if anything, lent validity to the result since misdiagnosis is less an issue among children with more extreme manifestations of any condition. However, in this situation, the need to seek medical care to be classified with ADHD raises a question of the characteristics of parents who bring their younger child for healthcare intervention. Almost surely, parents with this degree of sensitivity and health-seeking behavior would differ from parents who didn't bring their child to medical attention, but it is not clear whether such mothers would have been more likely or less likely to use APAP and thus the direction of such bias (toward or away from the null).

Follow-up only to age 3 would miss many ADHD diagnoses. Most children manifest ADHD by age 12, but relatively few are diagnosed prior to school age. Data from the CDC indicates that the prevalence of diagnosed ADHD is 2% among 3–5-year-olds, 10% among 6–11-year-olds, and 13% among 12–17-year-olds. Moreover, some children who appear to have ADHD and hyperkinesis early in childhood will subsequently be diagnosed with another condition. Because

this misclassification would not have been based on maternal APAP recall, it would have led to non-differential misclassification and bias toward the null, i.e., underestimation of true risk.

Exposure misclassification of APAP use was a concern both due to maternal forgetting and because the main findings were based on an ever/never classification of APAP use. These concerns were limited in the analyses of longer-duration users who probably would have less likely forgotten use. It was also limited by connecting the question on analgesics to indications for analgesic use. However, in the analyses of ever/never use, exposure misclassification likely occurred particularly because the question was open regarding any medication use in situations of fever/pain. As a result, women exposed and unexposed would have been admixed, diluting any real association and underestimating the true effect.

The Ystrom (2017) authors took particular care to adjust for indications for taking APAP. In addition to adjustment in models, they stratified their results by indication. Although Ystrom (2017) adjusted for many important potential confounders, unadjusted confounding must be considered in any epidemiologic study, no matter how excellent the design.

The Ystrom (2017) authors also assessed genetic confounding by using NCEs. One was preconceptual use of APAP, in the six months prior to pregnancy. The genetics of mothers would not change over the course of pregnancy. Thus, finding that preconceptual use was not associated with ADHD in a mother's offspring lent support to the role of APAP in the absence of invariant genetics. In fact, this finding particularly strengthens the argument supporting APAP as a causal factor in the genesis of ADHD because use in the six months before pregnancy and in the period during pregnancy were likely correlated (if a mother took lots of APAP she would be expected to do so in both time periods). Thus, the specific association with prenatal but not preconceptual use is striking.

On the other hand, the fact that paternal use of APAP in the six months before pregnancy was associated with ADHD is odd. I agree with the Court that "there is no reason to expect that paternal use of acetaminophen during pregnancy varies compared to paternal use of acetaminophen before pregnancy (time-invariance), or that it could cause a neurodevelopmental disorder in offspring (because conception has already occurred)." (Order at 21). It would be hard to explain biologically and, as noted below, is easier to explain behaviorally. Paternal use was queried for the timeframe of six months before pregnancy, not during pregnancy. Asked during a non-pregnancy interval, it simply suggests that paternal users of APAP were more likely to father ADHD children, perhaps because of behavioral correlations in taking medications and raising children. However, taken together with the maternal data, which showed that mothers taking APAP during the six-month preconceptual window did not show this correlation, suggests that mothers did not show behavioral correlations between medication taking and rearing an ADHD child.

More importantly, the association between paternal APAP use and ADHD was likely not an appropriate NCE for genetic confounding. How would a father's use reflect a mother's genetics? Why would such an association detract from the fact that only during the pregnancy was maternal use of APAP related to a childhood ADHD diagnosis? Surely the mother's genetics were not correlated with the father's genetics. The mother's behaviors might have been correlated with the father's, but even that is the opposite of the results presented.

Finally, as suggested by Thomas Frisell in a commentary published in the prestigious *American Journal of Epidemiology*, which addressed studies that had internally inconsistent results using designs for control of genetics: "If this rejects the causal hypothesis that prenatal smoking is associated with ADHD, then why is there such a clear dose-response pattern, and why did

some but not all negative control studies find an association specific to maternal vs. paternal smoking? When evidence seems conflicting, standard adjustment for potential confounders, demonstrating whether or not each could explain the association between exposure and outcome, has superior interpretability." (Frisell 2021) In other words, internally inconsistent results such as these are hard to interpret and should not be overinterpreted in the absence of other (adjustment) evidence of genetic confounding.

Overall, Ystrom (2017) showed a number or significant associations, particularly for long-term APAP use. Risks were on the order of 20 to 30% for use in two and three trimesters respectively. Risk elevation was 220% for >28 days of use. Several biases would have led to underestimation of observed risks. Ystrom also found an interaction between fever/infection and APAP use. An oddity in their results is that APAP use among fathers also led to more ADHD diagnoses.

Ji (2018)

This study examined maternal plasma biomarkers of APAP intake and ADHD diagnosis in the Boston Birth Cohort. 1180 children at birth who continued to receive their medical care at the Boston Medical Center were followed prospectively via record linkage within an electronic medical record database. ADHD diagnosis (N=188) was obtained based on electronic medical records. Maternal biomarkers of APAP use were measured in plasma samples obtained within 1 to 3 days postpartum.

Of 3098 children enrolled in the postnatal follow-up study of the Boston Birth Cohort, 1412 mothers had sufficient plasma samples for metabolomic assay. After excluding those with missing interview data, 1180 mother/infant pairs with all pertinent data were analyzed. This participant sample was like the excluded sample in terms of baseline maternal and newborn

characteristics, except for having a slightly higher percentage of Black children, longer gestation, and higher birthweight.

Exposure to APAP during pregnancy was measured by liquid chromatography-tandem mass spectrometry (LC-MS). The main metabolites of acetaminophen included unchanged acetaminophen (~5%), acetaminophen glucuronide (52–57%), acetaminophen sulfate (30–44%), and hepatotoxic N-acetyl-p-benzoquinone imine (NAPQI) (5–10%). NAPQI can be further detoxified as 3-(N-Acetyl-L-cystein-S-yl) acetaminophen.

Outcomes were based on ICD-10 diagnosis of ADHD. Children without any diagnosis of ADHD, ASD, or developmental delay were considered unaffected or neurotypical.

Covariates Models were maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, drinking during pregnancy, parity, maternal pre-pregnancy BMI, baby's sex, delivery type, gestational age, birthweight, maternal fever during pregnancy, intrauterine infection/inflammation, and breastfeeding.

In the final sample, there were 188 (11.9%) children with a diagnosis of ADHD, 44 (3.7%) children with a diagnosis of ASD (without ADHD diagnosis), 344 (29.1%) children with a diagnosis of other DD, and 604 (51.2%) neurotypical children. Compared to unaffected children, the authors reported a significant positive dose-response association with ADHD diagnosis for each maternal APAP biomarker, after adjusting for indication of APAP use and other pertinent covariates. Compared to levels in then non-detection category, below median and above median levels of maternal acetaminophen were associated with a 58% and 88% increase in the odds of ADHD diagnosis, respectively (OR below median 1.58, 95% CI 1.02–2.46; OR for above median 1.88, 95% CI 1.18–3.00). These estimates suggest a dose-response based on

APAP concentration. Stratification by covariates showed interaction effects; for example, mothers with a prenatal infection had an OR of 2.81 versus without infection of 1.57. In that the group without infection still had a significant increase in risk, this does not denote confounding but instead interaction.

Ji Critique

The Ji (2018) authors interpret their study as follows. “In this prospective birth cohort study, we found a significant positive association between maternal blood acetaminophen metabolite levels measured within 1–3 days postpartum and ADHD diagnosis in offspring.” They support their use of post-delivery plasma levels as a valid proxy despite their admission that the measure has only a 2–3-hour half-life and was measured 1-3 days postpartum, reflecting peripartum use (in the period around delivery). Specifically, they say: “Nonetheless, women with detectable levels of acetaminophen biomarkers are likely to be more regular users,” and “[O]ur evidence drawn from the perinatal period lends further support for the association between maternal acetaminophen use and ADHD in offspring.” (Ji 2018)

Critics of the Ji (2018) study have argued that the Ji result may reflect peripartum (around the time of delivery) exposure but not exposure earlier in the pregnancy—a possibility highlighted by the study authors as well. However, it is logically difficult to understand why a few doses at the time of delivery would be associated with a strong ADHD risk. Indeed, if this were the case, it underscores the likelihood that third trimester use is strongly linked to risk.

Confounding in this study, as the Ji (2018) authors note, was better addressed than in many other studies. They say: “This association remained after adjusting for multiple previously identified potential confounders and potential indications for acetaminophen use,” and “This association remained even after adjusting for indication factors of acetaminophen use (maternal

fever and maternal intrauterine infection/inflammation during pregnancy) and other pertinent covariates." (Ji 2018)

Reinforcing the support this study lends to the APAP and ADHD association, the authors underscore their finding of a dose response: "[W]e identified dose-responsive patterns across all acetaminophen metabolites and burden." (Ji 2018)

However, Ji (2018) notes their study is limited in its ability to adjust for genetics and familial aggregation: "[A]lthough we adjusted for major known risk factors of ADHD and indication of acetaminophen use, we could not adjust for several familial factors identified in previous studies. We also cannot rule out the possibility of unmeasured or unknown residual confounding, although our propensity score analyses seek to adjust for such confounding and provide additional credibility for our findings."

My review revealed that strengths of this study were the use of a biomarker of APAP exposure and a "hard" outcome of ADHD based on diagnoses from medical records. Consideration was given to confounding by indication. Although power was limited by the relatively modest number of women enrolled, it appeared to be sufficient to demonstrate significant associations.

Despite these strengths, the study had some notable limitations, as the authors are aware. APAP has a short half-life (2–3 hours) and thus would have only been detected within 24-48 hours of use. This would have greatly underestimated exposure and limited the exposure window to the end of the third trimester.

Reliance on hospital electronic medical records within a single hospital system would have meant that outcomes in families going elsewhere for their care would not have been captured

within the study. Whereas the prevalence of children diagnosed with ADHD were like national estimates for 7-year-olds, the proportion with other developmental disorders was high, suggesting that families with risk factors for neuroatypical children may have remained in the system. But the Boston Medical Center may have had specific facilities that cared for such children, leading to their overrepresentation. Because reporting of APAP use during pregnancy would not be expected to differ by the patient mix, this would have affected generalizability (to a group of children with more risk for ADHD) but not bias. With respect to confounding, no adjustment was made for genetic factors or for maternal co-morbidities, such as depression/anxiety known to contribute to ADHD risk.

Thus, Ji (2017) demonstrated a 58% and 88% increase in the odds of ADHD diagnosis associated with APAP exposure. For mothers using APAP and having a prenatal infection, the risk was as high as a 280% elevation. The Ji (2017) study was appealing for its use of a biologic measure of APAP exposure. Despite its limitations, the fact that it took a different tack to establishing an association between APAP use and ADHD lent a new dimension to the literature.

Chen (2019) Chen (2019) conducted a case-control study nested within an electronic medical record system. The authors examined APAP use during pregnancy and ADHD risk among 950 women/child pairs with ADHD and 3,800 control pairs matched by demographic characteristics from the Taiwan Longitudinal Health Insurance Database. The database reflects information from a compulsory and universal health insurance program offering comprehensive medical care coverage to all residents of Taiwan.

Children born between January 1, 1998, and December 31, 2008, who received diagnoses of ADHD (ICD-9-CMcode: 314) by board-certified psychiatrists, based on diagnostic interviews

and clinical judgement, were included as cases. Randomly-selected, population-based controls were matched to cases in a ratio of 1:4 based on the mother's age, offspring sex and ages, mother's age during pregnancy, income, and urbanization level.

APAP use and gestational infections were assessed in the first trimester, second trimester, and third trimester, and during the pre-pregnancy period from 3 months before pregnancy to the date of last menstrual cycle. Cumulative dose (mg) of APAP was calculated in each trimester. The Chen (2019) authors give no details as to how exposure was ascertained but likely it was a variable within the database or calculated based on dosage and recommended frequency at the time of prescribing. They also give no information on how calculations were made. Both of these omissions make it difficult to assess the validity of the exposure metric.

Confounding factors included gestational infections (respiratory, urinary tract, gastrointestinal, and sexually transmitted infections). Maternal mental health disorders, including schizophrenia, bipolar disorder, and major depressive disorder, were captured from the database, as was medication use, including antidepressants, mood stabilizers, atypical anti-psychotics, ADHD medications, and benzodiazepines. Preterm or low birth weight, birth trauma, and intrauterine hypoxia/birth asphyxia were also assessed. Thus, adjustments for confounding by maternal or neonatal conditions were extensive and more comprehensive than in many other studies.

After adjustment for potential confounders, APAP use in any trimester was associated with ADHD risk (RR 1.20, 95% CI 1.01–1.42), a result which grew stronger after excluding women with gestational infections and maternal health disorders (RR 1.40, 95% CI 1.14–1.73). Second trimester exposure to APAP was associated with a significantly increased risk of ADHD (OR 1.19, 95% CI 1.00–1.40). Similarly, elevated risk was seen for use in both first/second trimesters (OR 1.28, 95% CI 1.00–1.64). Sensitivity analysis excluding women with gestational infections

and maternal mental health disorders confirmed, and even slightly strengthened the associations for second trimester (OR 1.33; 95% CI 1.04–1.69) and first/second trimesters (1.68, 1.18–2.40). However, risks were not elevated for third trimester exposure alone or in combination with other trimesters.

Chen Critique

The Chen (2019) authors interpretated their findings as: “Prenatal exposure to acetaminophen, especially in the second trimester, was associated with an increased risk of ADHD in offspring.” They commented on their consideration of confounding, noting that, “The association between acetaminophen exposure and ADHD risk was independent of gestational infections or maternal mental health disorders.” (Chen 2019)

“However,” they say in their discussion of limitations, “our study did not identify a dose-dependent relationship between prenatal acetaminophen use and the offspring’s ADHD risk; the log-transformed maternal cumulative doses of acetaminophen were not related to ADHD risk in off-spring.” (Chen 2019)

This is one of the few case-control studies published in the APAP and ADHD literature. Like all case-control studies, it suffers from the potential for selection bias. Recall bias was not a problem, as the study used data from a comprehensive database. Similarly, temporality problems in which outcome preceded exposure, rather than the other way around, was unlikely since the database tagged information by date. Because it was nested within a prospective data collection system, it thus did not suffer from the problems inherent in case-control studies based on recall.

Strengths of the study were its use of a mandatory, complete information source for all of Taiwan. Another strength was outcome determination by psychiatrists.

The number of children with outcomes was large, a good deal larger than in many of the cohort studies. Matching on several characteristics and then adjusting for many others was also a strength.

A major study weakness was (like its strength) reliance on a record database. This source meant that only the most severe cases of ADHD would have been captured. Because some subjects in the control group may have had ADHD that was not identified, non-differential misclassification may also have occurred, biasing study findings toward the null. After exclusion of women with maternal co-morbidities, results were more pronounced.

Reliance on the database for APAP exposure was an even more concerning issue. APAP is generally available without prescription in Taiwan, and OTC use was not assessed. However, because the national health insurance program is free, many women may have sought a prescription rather than paying out of pocket. Fully three quarters of participants used APAP during at least one trimester of pregnancy, suggesting that database reliance may not be a fatal flaw in the design.

The Chen (2019) study also failed to replicate the association between third trimester APAP use and ADHD. In fact, the trimester analyses, particularly those looking at use in more than one trimester, were apparently based on small sample sizes since they had wide confidence intervals, detracting from their precision. In this sense, the most robust and likely valid measure of APAP use was use in any trimester.

Chen (2019) also failed to control for genetic and other sources of unmeasured confounding.

Overall, as a case-control study, Chen (2019) might be considered *a priori* to be a weaker design than a prospective study. However, in that it was nested within a prospectively collected database, it did not suffer from many other biases normally found in case-control designs. The study's results indicated that APAP use in any trimester increased ADHD risk modestly but significantly and by about 40% after excluding women with gestational infections and maternal mental health disorders.

Liew (2019)

One of the more unusual studies in the APAP and ADHD literature, the Liew (2019) analysis employed a NCE approach using data from the Nurses Health Study II (NHS II). NHS II is a large cohort of participating nurses study conducted between 1993 and 2005. The authors used the NCE of APAP use in the period "a few years before" and "a few years after" pregnancy to detect suspected and unsuspected genetic and other confounding. These NCE variables should not causally affect the outcome but shared a similar confounding structure with the exposure variable of interest. Moreover, maternal use outside of the prenatal window biologically reflected the mother's genetics, as well as other invariant factors such as socioeconomic status.

In 1989, NHS II enrolled nurses from throughout the U.S. at 25 to 42 years of age. 116,430 female nurses were recruited and followed biennially with questionnaires. Mothers were asked whether during the previous 2 years they had used APAP regularly (defined as ≥2 times/week in the 1989 and 1993 questionnaires and ≥1day/week from 1995 onwards). Ever/never regular maternal APAP use was reported on the questionnaire during the year of the child's birth. Notably, the exposure question was not about use specifically during pregnancy and the design could not capture whether, when, and how often APAP was used during the prenatal period.

The outcome of ADHD relied on the question, “have any of your biological children been diagnosed with attention-deficit/hyperactivity disorder (ADHD)?” and the year of birth of any child diagnosed with ADHD. (Liew 2019) To assess the validity of this measure, a previous study among 92 children reported as having ADHD in NHS II scored high on the ADHD Rating Scale, including inattention and hyperactivity-impulsivity. Girls scored above 90%, and boys scored above 80%; a further 63.8% of boys scored above 90%. As the ADHD Rating Scale is known to correlate highly with ADHD diagnoses, this validation study is reassuring.

Adjustment was made for the following covariates: Maternal age at the child’s birth (<30, 30–34, 35–40, or >40 years); child’s birth order (first, second, third, or fourth or later); child’s birth year; maternal gestational diabetes; preeclampsia; and self-reported regular maternal use of aspirin or aspirin-containing medication or other nonsteroidal anti-inflammatory drugs.

NCE control consisted of comparing ADHD risk for maternal use of APAP at the time of pregnancy to use “a few years before” and “a few years after pregnancy.” (Liew 2019)

Regular maternal APAP use during the three defined exposure periods was moderately correlated (Spearman’s r=0.28–0.32). In models with APAP use in all exposure periods included only maternal APAP use in the year of the pregnancy was associated with elevated odds of ADHD in offspring (OR 1.34, 95% CI 1.05–1.72). Among women who reported they were pregnant at the time they completed the questionnaire, the association with ADHD was somewhat greater (OR 1.46, 95% CI 1.01–2.09), while use in the other periods remained null. There was a similar, though not statistically significant, result reported in a differently adjusted model for women who reported they were pregnant at the time they completed the questionnaire. (OR 1.39 95% CI 0.99–1.95) The positive association between APAP use at the

time of pregnancy but not in the other exposure periods and ADHD in offspring remained largely unchanged in: (a) analyses restricted to mothers with no depression, rheumatoid arthritis, or migraine headache; (b) analyses excluding mothers who used aspirin and other nonsteroidal anti-inflammatory drugs at the time of the pregnancy; and (c) in analyses adjusting for demographic factors.

The correlation between APAP use in the different time periods was modest, suggesting that behaviors varied over time. The weak correlation also suggests that time-invariant factors, such as genetics, had a weak or null impact on medication-taking behavior. If genetics strongly affected medication-taking, one would expect that since genetics does not change over time, then APAP use would not change over time. Yet, the data showed that it does.

Moreover, the presence of an association between APAP use and subsequent ADHD diagnosis in the pregnancy window, but not in the pre-pregnancy and post-pregnancy periods, precludes the possibility of genetics in that given woman as an explanation for the APAP-ADHD relationship. It also precludes other time-invariant potential confounders, such as maternal chronic diseases or socioeconomic status. Since these are unlikely to change markedly over a short time span, they do not explain the association observed for APAP exposure at the time of pregnancy.

Liew Critique

The Liew (2019) authors described their overall results as: “Our NCE analysis suggested that only acetaminophen use at the time of pregnancy was associated with childhood ADHD (odds ratio = 1.34, 95% confidence interval: 1.05, 1.72), and the effect estimates for the 2 NCE periods (about 4 years before and 4 years after the pregnancy) were null.” “The findings of our

NCE analyses corroborate those of prior reports suggesting that prenatal acetaminophen exposure may influence neurodevelopment." (Liew 2019)

They point out that their design was meant to exclude genetic and other time-invariant confounding, writing that, "the absences of associations with acetaminophen use in the pre-pregnancy and post pregnancy periods are the true NCE tests and they suggest that variables that do not vary over a few years—such as genetics, maternal chronic diseases, or socioeconomic status—do not explain the association observed for acetaminophen exposure at the time of pregnancy." (Liew 2019)

Nonetheless, Liew (2019) was aware of the study limitation of lack of adjustment for confounding by indication: "However, we cannot rule out the possibility of other un-controlled risk factors for ADHD that are uniquely correlated with the use of acetaminophen during the pregnancy period. One possible candidate could be conditions like fever, infections, or mild pain. However, such conditions should have led to sporadic use of acetaminophen, if any; our exposure variable was regular use of acetaminophen. Thus, confounding from this source would seem less likely." The Liew (2019) authors also indicated that unaccounted confounding by other, unadjusted time-varying factors specific to pregnancy may have impacted their results: "Future investigations are still needed, especially studies with improved exposure and outcome assessment and studies with the ability to address known and possibly unknown confounding factors in the analyses."

The Liew (2019) study is unique in using the structure of NHS II, which would not facially be an obvious database in which to study the APAP and ADHD question. NHS II was not originally constructed to study pregnancy-related exposures. Questionnaires did not specifically cover the pregnancy period and were completed only biennially. However, for a NCE analysis it provided

an unusual opportunity to use the time periods before and after pregnancy to demonstrate that covariates that did not change over time were unlikely to have accounted for the APAP and ADHD association. Genetics, for instance, would not change over time and if it drove the APAP-ADHD relationship, it should have done so consistently over time, yet only in the biennial window in which the pregnancy occurred was APAP use related to ADHD.

Other Liew (2019) study strengths include the cohort design, large sample size, and adjustment for confounders, in addition to the NCE analyses. Maternal report of the ADHD outcome would be a substantial concern, but the authors took care to perform a validation study showing the measure to correlate strongly with a gold standard assessment.

There were, however, several weaknesses. The assessment of APAP was crude at best, relying on self-report of ≥2 times/week or ≥1 day/week during the previous 2 years. On the other hand, that exposure variable would suggest chronic use and perhaps, then, chronic use during pregnancy. This is because the question was about “regular,” not just any, APAP use. The fact that women may not have been pregnant anywhere near the time of the questionnaire is a concern. However, Liew (2019) repeated the analysis for women who reported they were pregnant at the time of the questionnaire and got similar, indeed somewhat enhanced, results. Moreover, the crudeness of the ever/never chronic use variable would have biased results toward the null.

Another concern is the age distribution of the cohort. NHS II was designed to follow women into menopause and thus has an older age structure than would be desired for a pregnancy cohort. The youngest women were 30 so that many of the births would have occurred among older mothers. Maternal age is a risk factor for ADHD so age may have biased the sample, although it is not clear that older mothers have different patterns of APAP use.

Finally, although the NCE analyses would have controlled for fixed confounders, it would not have controlled for time-variant factors. Thus, potential factors such as maternal fever/infection may still have confounded the results. Also, the list of confounding variables was limited and did not include many indications, familial aggregation factors, or socioeconomic factors.

Overall, the Liew (2019) study provided a fascinating and unique methodology to adjust for time-invariant confounding. Despite likely bias toward the null, the authors found an association between APAP use on the order of a 34 to 46% increase in risk.

Baker (2020)

In a uniquely robust study employing a biologic measure of exposure and a hard measure of outcome, Baker (2020) examined the association between prenatal APAP exposure measured in meconium and ADHD in children aged 6 to 7 years, along with functional brain connectivity.

The study was embedded in a prospective birth cohort from the Centre Hospitalier Universitaire de Sherbrooke in Sherbrooke, Québec, Canada. 394 children were eligible for inclusion, of whom 345 (88%) had meconium samples collected at delivery, as well as information on physician diagnosis of ADHD. Mothers were enrolled between 2007 and 2009, at their first prenatal care visit or delivery and were followed up when children were aged 6 to 7 years. When children were aged 9 to 11 years, a subset were enrolled in a sub study testing resting-state brain connectivity with magnetic resonance imaging. Forty-eight children had been tested at the time of this analysis.

Exposure assessment was APAP measured in meconium removed from diapers of newborns and analyzed with ultraperformance liquid chromatography mass spectrometry (LC-MS). APAP

was detected in 199 of the 345 samples (57.7%), with a method that recovered virtually all chemical moiety and was highly replicable (repeatability of ±15%).

Several outcomes were employed. At a scheduled cohort follow-up when children were aged 6 to 7 years, parents were asked on a questionnaire if their child had physician-diagnosed ADHD. In total, 176 parents provided information at the 6- to 7-year follow-up. For those who did not complete the 6- to 7-year follow-up visit (n = 169), physician diagnosis of ADHD was obtained from reviewing medical records from Centre Hospitalier Universitaire de Sherbrooke pediatric clinics, which are available in the hospital database.

In addition, among the 48 children in the MRI analysis subsample, 46 completed the Behavioral Assessment System for Children Parent Report Scale (BASC3-PRS) at ages 9 to 11 years. In the BASC3-PRS, parents answer a range of questions concerning the behavior of their children that are combined into various rating scales, including scales for attention problems and hyperactivity.

MRI data involved resting-state analyses that focused on connectivity in 3 classical brain networks often implicated in ADHD: the default mode, salience/cingulo-opercular, and frontoparietal/central executive networks.

Confounding factors considered in models included child sex, family income, and maternal age at delivery, educational status, pre-pregnancy BMI, smoking during pregnancy, and alcohol use during pregnancy. A sensitivity analysis, including self-reported ADHD in the mother, was an additional covariate.

In addition to reporting the results of logistic regression models, adjusted for potential confounders, the Baker (2020) authors employed causal mediation analysis to test for mediation of the association between prenatal acetaminophen exposure and hyperactivity by resting-state brain connectivity. This approach uses a quasi-Bayesian Monte Carlo method with 1000 simulations, to test whether connectivity mediated the association between prenatal APAP exposure and hyperactivity. The average direct effect and average causal mediation effect are computed, reflecting direct and indirect (i.e., mediated by connectivity) effects of prenatal APAP exposure on hyperactivity. Information from two models is compared: (1) connectivity as outcome and prenatal APAP level as a covariate, and (2) hyperactivity as outcome and both connectivity and prenatal APAP level as covariates.

Among the 345 children included in the analysis (177 boys [51.3%]), APAP was detected in 199 meconium samples (57.7%), and ADHD was diagnosed in 33 children (9.6%). Compared with no APAP, detection of APAP in meconium was associated with increased risk of ADHD (OR 2.43; 95% CI 1.41–4.21) in a weighted sample balanced on covariates. APAP exposure was then categorized into 3 levels. High levels of acetaminophen detected in meconium increased the odds of ADHD more than 4-fold (OR, 4.10; 95% CI, 2.41–6.95). A dose-response association was detected; each doubling of exposure increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02–1.19).

Children with APAP detected in meconium showed increased negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices. Children with decreased connectivity were more hyperactive ($p = .03$). Causal mediation analysis revealed no total or direct effect of meconium APAP levels on hyperactivity, but a significant indirect effect on increased hyperactivity mediated through frontoparietal network and right precentral/frontal gyrus connectivity (14%; 95% CI, 1%–26%).

The Baker (2020) authors conclude: “By using a direct measurement of prenatal acetaminophen exposure that is unbiased by maternal recall, these results add evidence in support of the association between prenatal acetaminophen use and child ADHD. Taken together with the large ORs reported in the Boston Birth Cohort study, these results suggest that prior studies may have been biased toward the null by inaccurate maternal recall. Thus, the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated.”

Baker Critique

The Baker author’s (2020) description of their results were that “children exposed to acetaminophen prenatally were at increased risk of ADHD at ages 6 to 7 years.” They described meconium as, “A direct measurement of fetal acetaminophen exposure that reflects longer-term exposure throughout pregnancy.” (Baker 2020) Moreover, they note that their analysis found evidence of a dose-response. “Categorical and continuous models suggested that higher levels of meconium acetaminophen increased the risk of ADHD in children in a linear manner.” (Baker 2020)

One of the Baker (2020) study’s strengths, in comparison to other designs, was its lack of reliance on recall. Recall was likely similar in mothers of ADHD children and mothers of unaffected children, particularly insofar as APAP was considered safe during pregnancy. Misclassification of APAP use would have biased results toward the null and thereby diluted the observed risk in other studies but not in Baker (2020). The Baker (2020) authors points this out: “All but 1 of the prior studies of the association between prenatal acetaminophen exposure and child ADHD have relied on questionnaires requiring mothers to recall drug use at intervals greater than 3 months. Difficulty recalling drug use during pregnancy may result in nondifferential misclassification bias toward the null. This source of bias may explain the smaller

pooled risk ratio of 1.34 for ADHD from past cohort studies compared with the nearly 2.5-fold increased odds reported herein." "Thus the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated." (Baker 2020)

Although the Baker (2020) authors underscore the study's main strength, they also acknowledge a major limitation in lack of adjustment for confounding by indication or genetics. Their analysis suggests that this is not a fatal flaw: "Although we did not control for indications for acetaminophen use in this study, prior cohort studies controlling for maternal fevers, infections, and other indications for acetaminophen use have reported lack of confounding by these factors." (Baker 2020) Moreover, "Another possibility is confounding by unknown genetic, social, and familial factors associated with acetaminophen use. This concern has been recently addressed with negative control exposure analysis: maternal acetaminophen use before and after pregnancy and a partner's acetaminophen use were not associated with child ADHD in populations in which maternal acetaminophen use during pregnancy increased the risk." (Baker 2020) They also point out: "Although meconium is known to accumulate drugs and drug metabolites throughout the last two-thirds of pregnancy, we did not explicitly correlate maternal acetaminophen use with acetaminophen concentrations in meconium, a potential limitation that should be the subject of future work." (Baker 2020) Notably, they subsequently completed that work and directly showed that APAP in meconium was a stronger indicator of ADHD risk than maternal recall. (Laue 2018)

The Court's Order called Baker (2020) a "well-regarded study." (Order at 85) The Court did, however, ask plaintiffs' counsel to explain why the wide confidence interval (2.43, 1.41–4.21) does not "undercut its reliability." (Order at 85) The answer is that confidence interval indicates the reproducibility of a result, so specifically here the finding is that if the study were repeated 100 times, the result would fall 95 times in the range of 1.41 to 4.21, i.e., a risk elevation of from

40 to 320% increase. That range always reflects a positive result and one that clearly excludes 1.0. The range is relatively wide because the sample size is relatively small. Yet even the modest study size clearly precludes a null interpretation.

The Baker (2020) study thus has many strengths. Both exposures and outcome measures (in a subset) were based on hard data. The overall outcome of ADHD was based on a question about physician diagnosis or determined by medical record review.

Exposure based on fetal meconium circumvents both the problem of under-recall and the problem of the short half-life of APAP in plasma. Meconium is known to accumulate drugs and drug metabolites throughout the last two-thirds of pregnancy, representing an excellent measure of maternal use. Moreover, it reflects not just what the mother ingested but what the fetus was exposed to. The biologic measure also provides an opportunity to look directly at dose-response and the study found higher levels of APAP in meconium to yield greater ADHD risk. However, the stronger effect sizes found here, as compared to effects found in recall-based studies, suggests that with a more precise exposure measure, the association between APAP use in pregnancy and ADHD has been previously underestimated.

The use of MRI scanning validated the ADHD diagnosis and provided information on a possible biologic pathway linking APAP use to ADHD. Disruption of the connection between the frontal lobe and default mode network nodes to clusters in the sensorimotor cortices has been demonstrated as a putative mechanism for hyperactivity and was shown as an indirect mediator here.

The main weakness of the study, as the Baker (2020) authors note, was limited adjustment for confounding. Neither confounding by maternal indication nor by genetic or familial aggregation

factors was considered. This raises the possibility that unadjusted confounding may have impacted (either positively or negatively) the results.

Overall, the Baker (2020) study is one of the strongest in the APAP and ADHD literature. The risk of ADHD associated with exposure to APAP, as measured by fetal meconium, was 2.4, and for high levels of APAP, it was 4.1. Moreover, APAP exposure was associated with disruptions in frontal lobe connectivity by MRI scanning that have been (and were in this study) associated with ADHD hyperactivity.

Ji (2020)

Like the earlier Ji (2018) study, the 2020 Ji analysis was embedded in the Boston Birth Cohort. Cord blood was used as a biological marker for exposure to prenatal APAP. 1180 children at birth who continued to receive their medical care at the Boston Medical Center were followed prospectively via record linkage within an electronic medical record database. ADHD diagnosis (N=188) was obtained based on electronic medical records.

Of 3098 children enrolled in the postnatal, follow-up study of the BBC, after excluding those with missing interview data, 996 mother/infant dyads had archived cord blood collected at birth and were included in this analysis.

Three cord acetaminophen metabolites (unchanged acetaminophen, acetaminophen glucuronide, and 3-[N-acetyl-L-cystein-S-yl]-acetaminophen) in cord plasma samples were measured by liquid chromatography-tandem mass spectrometry (LC-MS). The main metabolites of acetaminophen included unchanged acetaminophen (~5%), acetaminophen glucuronide (52–57%), acetaminophen sulfate (30–44%), and hepatotoxic N-acetyl-p-benzoquinone imine (NAPQI) (5–10%). NAPQI can be further detoxified as 3-(N-Acetyl-L-cystein-S-yl)

acetaminophen. All cord samples had detectable unchanged acetaminophen. Among children whose maternal acetaminophen exposures were in the first tertile, more than 60% had second and third tertile cord unchanged acetaminophen exposure. This phenomenon may reflect the differences in metabolic capacity for acetaminophen between adults and neonates.

Outcomes were based on ICD-10 diagnoses of ASD, ADHD, developmental delays, or intellectual disabilities. Children without any of these diagnoses were considered unaffected or neurotypical.

Covariates were maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, drinking during pregnancy, parity, maternal pre-pregnancy BMI, baby's sex, delivery type, gestational age, birthweight, maternal fever during pregnancy, intrauterine infection/inflammation, and breastfeeding.

Of 996 participants (mean age, 9.8 years; 548 [55.0%] male), the final sample included 257 children (25.8%) with ADHD only, 66 (6.6%) with ASD only, 42 (4.2%) with both ADHD and ASD, 304 (30.5%) with other developmental disorders, and 327 (32.8%) who were neurotypical. Unchanged APAP levels were detectable in all cord plasma samples. Compared with being in the first tertile, being in the second and third tertiles of cord acetaminophen burden was associated with higher odds of ADHD diagnosis (OR for second tertile, 2.26, 95% CI 1.40–3.69; OR for third tertile, 2.86, 95% CI 1.77–4.67). Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen burden and ADHD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex, for which point estimates for the ORs vary from 2.3 to 3.5 for ADHD. Cord blood APAP was not associated with other developmental disabilities.

Ji Critique

The Ji (2020) authors stated that their results showed: “Cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD in a dose-response fashion.” They asserted that umbilical cord plasma is a valid proxy for recall of APAP use. “The cord plasma metabolites provide a direct measurement of fetal acetaminophen exposure before delivery.” (Ji 2020) Moreover, they suggest that this unique approach to exposure measurement supports prior evidence for an APAP and ADHD link. “Our findings support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk and warrant additional investigations.” (Ji 2020)

With respect to confounding, the Ji (2020) authors state: “The positive associations between cord acetaminophen and ADHD and the cord acetaminophen and ASD were observed across strata of pertinent covariates, including maternal fever during pregnancy, which is an indicator for acetaminophen use. The associations also persisted after a series of further adjustment of potential confounders and differential inclusions.”

Moreover, they discuss their dose response findings as follows: “Furthermore, there were dose-response patterns for cord uncharged acetaminophen and cord acetaminophen burden with the risk of ADHD and ASD.” (Ji 2020)

Nonetheless, the Ji (2020) authors are aware of their study’s limitations: “The present study has some limitations. First, it only included a 1-time measurement of cord acetaminophen metabolites at birth. Given that the half-life of acetaminophen in adults is less than 3 hours, the cord plasma measurement may at most reflect maternal use of acetaminophen during the peripartum period.” They also note that “because of our observational study design, we were

unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors." (Ji 2020)

Like the Ji (2018) report, the Ji (2020) report has several notable strengths. The use of cord blood for measurement of APAP makes it one of the few studies with a biologic measure of exposure. Cord blood represents not just APAP that the mother ingested but the concentration to which the fetus was directly exposed. The study also used a "hard" outcome of ADHD based on diagnoses from medical records. Although power was limited by the relatively modest number of women enrolled, because the diagnosis of ADHD was substantial, there was sufficient power to demonstrate significant associations.

Despite these strengths, the study had several limitations, many of which were emphasized by the ENTIS authors when critiquing the Consensus Statement. As the Ji (2020) authors acknowledge, APAP has a short half-life (2-3 hours) and thus would have only been detected within 24–48 hours of use. This would have greatly underestimated exposure and limited the exposure window to the end of the third trimester. However, as the Ji authors noted in their 2018 report, "Nonetheless, women with detectable levels of acetaminophen biomarkers are likely to be more regular users." Overinclusion of women who may have taken APAP to dull the pain of delivery would have likely been non-differential between mothers who bore children later diagnosed with ADHD; such misclassification would have biased results toward the null, i.e., towards an underestimate of true risk.

Oddly, the Ji (2020) authors report that APAP was detected in all the cord blood specimens measured. It is unclear whether this represents over-detection or ultra-sensitive detection, since it has been shown that virtually everyone has minute quantities of APAP metabolites in their blood (due to water contamination). Nonetheless, since the analysis was based on internal

comparisons of tertiles, over-detection likely had little impact on the results. That is, the comparison of interest was an internal assessment of high vs. low APAP concentration, and concentrations in the high range as compared to the low range reflected risk. Said another way, in the absence of a causal link between APAP and ADHD, there is no reason that women with more APAP in their cords should have had children with ADHD at higher rates than women with less APAP in their cord specimens.

Reliance on hospital electronic medical records within a single hospital system would have meant that outcomes in families going elsewhere for their care would not have been captured within the study. As pointed out by Damkier (2022), a surprisingly large proportion of enrolled children were diagnosed with ADHD or ASD (37%), and only 33% of children had no 'developmental disability' diagnosis. Indeed, the proportion of children with ADHD or ASD or both was substantially higher and the percentage deemed neurotypical lower than in the Ji (2018) report for unclear reasons. The most likely explanation is selection bias, wherein mothers who had cord blood ascertained were more likely to bear an affected child. Since exposure preceded disease by several years, it is hard to imagine that the availability of samples somehow led to misclassification toward an overestimated result. Even if Ji (2020) selectively measured APAP in cord specimens selected based on later knowledge of disease, the authors would not have known the outcome of measurements. Again, this imparts skepticism to any suggestion that selection bias led to overestimation of the true effect.

With respect to confounding, few factors were considered in the analysis. No adjustment was made for genetic factors or for maternal co-morbidities, such as depression/anxiety known to contribute to ADHD risk. This was, indeed, a limitation of the study.

Thus, Ji (2020) showed large effect sizes linking APAP exposure to ADHD (a 286% increase in risk for the highest tertile). Although Ji's design and methods were unique in several ways and thus contribute a different dimension to the literature, the study's weaknesses must be acknowledged.

Gustavson (2021)

Once again using data from MOBA, Gustavson (2021) assessed the relationship between maternal APAP use and registry-based ADHD outcomes, using a sibling pair design. However, the ADHD-diagnosis of hyperkinesis reported here was more restrictive than that used by Ystrom (2017), such that only the most severe cases were captured; this may have resulted in a bias toward the null, in that the control group now contained more actually affected cases.

The same methods from MOBA regarding exposure measures and outcome measures (as described by Ystrom (2017) apply here. Given that the database had been updated since these earlier analyses, the numbers of subjects and length of follow-up had changed as follows: 21448 children; 19,641 in sibling pairs; 1807 in trios or quartets. It is unclear how this compares to the Ystrom (2017) analysis since the sample size in that paper combined children with mothers and fathers to give a much higher number. What is clear is that Ystrom (2017) was published four years before the Gustavson (2021) analysis, so some additional data on outcomes among older children would have been available. In Gustavson (2021), 748 children had received an ADHD diagnosis which presumably (not clear) refers to ADHD diagnoses made within sibling pairs. In Ystrom (2017), among all children with an ADHD diagnosis by age 3, 2246 children were reported to have ADHD. Here, Gustavson (2021) used a diagnosis up to age 15. This would have captured the great majority of children developing the disorder.

Siblings were discordant on exposure, as well as outcome, in 306 families. Siblings were discordant on exposure for 29 days or more in 380 families, and 34 of these were also discordant on the outcome.

After adjustment for potential confounding factors, children exposed to APAP for less than 28 days during pregnancy did not have increased risk of receiving an ADHD diagnosis; however, long-term exposure (29 days or more) was associated with a two-fold increase in the diagnosis (HR 2.02, 95%CI 1.17–3.25). In the sibling control model, the association between long-term APAP use and ADHD in the child was HR 2.77 (95%CI 1.48–5.05) at the between-family level but only HR 1.06 (95%CI 0.51–2.05) at the within-family level. In other words, using non-sibling controls resulted in an estimate of a 2-fold increase, but use of sibling controls appeared to eliminate (almost) all of the observed risk. Although the small risk of 1.06 remained positive, it was now no longer significant.

Gustavson Critique

The Gustavson (2021) authors summarized their results: “Long-term use was associated with a two-fold increased risk of ADHD diagnosis.” Moreover, “Both the exposed and the unexposed children of mothers with long-term use of acetaminophen in one of the pregnancies had increased risk of receiving an ADHD diagnosis. This indicates that the observed association between long-term acetaminophen use during pregnancy and ADHD in the child may at least partly be confounded by unobserved family factors.” (Gustavson 2021)

At the same time, they point out a major limitation in their analysis: “However, only discordant siblings contribute to detecting associations in sibling control models; thus, reduced power is reflected in wide confidence intervals.” (Gustavson 2021) “Measurement error may attenuate association estimates more in sibling control models than in analyses without sibling control, as

discussed above. This may lead to false conclusions that observed associations are due to familial confounding factors." (Gustavson 2021) They also note that, "the sibling comparison model adjusts not only for stable confounding factors, but also for potential mediating factors that affect all siblings even if only one is exposed (Sjolander & Zetterqvist, 2017). This may lead to underestimation of association estimates." (Gustavson 2021)

As a result of this limitation, the Gustavson (2021) authors caution: "As only discordant siblings contribute to information in sibling control models, even the current very large birth cohort provided limited statistical power. Hence, the results need to be replicated in other studies." Indeed, they repeat this concern: "the finding of similar risk for ADHD in siblings discordant for long-term maternal acetaminophen use must be interpreted with caution and needs to be replicated in other studies." (Gustavson 2021)

I concur with Gustavson's (2021) assessment. The MOBA database has both strengths and weaknesses that have been discussed above and I will not repeat here (see Ystrom 2017).

However, weaknesses specific to this report are several. The first is reliance on registries. Registries likely represented only children with more severe problems. Children with ADHD fall within a spectrum of modest symptoms that would not come to medical attention to more debilitating symptoms. Factors that limit this problem are that, first, Norwegian hospital registries also include outpatient clinic information. Second, national health insurance would have ensured access to these resources for the entire population. Third, inclusion of more severe cases would have, if anything, lent validity to the result since misdiagnosis is less an issue among children with more extreme manifestations of any condition. However, in this situation, the need to seek medical care to be classified with ADHD raises a question of the characteristics of parents who bring their younger child for healthcare intervention. Surely, parents with this degree of

sensitivity and health-seeking behavior would differ from parents who didn't bring their child to medical attention, but it is not clear whether such mothers would have been more likely or less likely to use APAP and thus what direction (toward or away from the null) the results are biased.

Importantly, the fact that such a small number of discordant sibling pairs was identified from such a large database suggests an extreme degree of selection bias. That is, if all sibling pairs were included, as Brandlistuen (2013) did (see below), the sample size would have been far larger. But here only sibling pairs with a yes/no diagnosis of ADHD were informative. That number was an unusual fraction of the whole sibling sample. Exacerbating this problem, Gustavson (2021) used a more rigorous definition of hyperkinesis. Thus, no matter which way the study was biased, it is unlikely to in any way represent the situation for other women with an ADHD diagnosed offspring.

Exposure misclassification of APAP use was limited by focusing on long-duration users but it still likely occurred, leading to non-differential exposure misclassification. Moreover, admixing less frequent and lower dose users with more frequent/lower dose users likely diluted dose-response effects. Once again, non-differential exposure misclassification would bias results toward the null.

When Gustavson (2021) acknowledges that, "the sibling comparison model adjusts not only for stable confounding factors, but also for potential mediating factors that affect all siblings even if only one is exposed" they are saying that, although the sibling design was conducted to limit genetic confounding, it may also have limited differential post-partum childhood environmental exposures. No two children share the same family environment. Birth order and parental behavior, just to name a few factors, change over time. Quite possibly, mothers of children who have developed symptoms of ADHD might avoid taking any medications, including analgesics in

the next pregnancy and may change other pregnancy and postnatal behaviors to limit any possible adverse exposures. Thus, siblings would not share pertinent environmental factors. Mothers who avoided use of APAP during a second pregnancy might also have been more likely to seek medical attention for a mildly affected yet unexposed sibling after the experience of the first sibling. This would, again, result in bias toward the null. Moreover, sibling controls do not exclude genetic factors since siblings share only 50% of their genes.

Epigenetic effects, not shared by siblings, might be an important aspect of the genetics of ADHD. This likely explains why first births are more likely to be affected by ADHD than subsequent births. Use of siblings as controls would not overcome this issue. Thus, sibling studies limit but do not exclude shared familial confounding.

To expand on the Gustavson (2021) author's own concerns about their analysis, siblings were discordant on exposure for 29 days or more in 380 families, and 34 of these were also discordant on the outcome. The most relevant group, driving the comparison, is the pairs discordant for both the exposure and outcome, as these would provide the equivalent of exposed vs. unexposed cases as compared to exposed vs. unexposed controls. Thus, effectively the whole Gustavson (2021) analysis rests on 34 pairs, a much smaller number than would be assumed given the large sample size. This small sample size led to large confidence intervals (within-family HR 1.06, 95% CI 0.51–2.05). This suggests that the effect could have been as little as half or as large as double. Such as wide interval provides little assurance about what the result would be if the study were replicated on a larger sample size.

In contrast, long-term *in utero* APAP exposure was associated with a 2.77-fold (95% CI 1.48–5.05) increase in risk at the between-family level ADHD at the between-family level. This result was based on a ten-fold larger sample size than the within-family analysis. Even this, however,

led to an imprecise result, suggesting that other, unrecognized factors, led to variation in the effect.

Overall, the Gustavson (2021) study raises a real concern about genetic confounding. However, as the Gustavson (2021) authors note more than once, their results must be considered cautiously. Multiple weaknesses in design were all in the direction of creating bias toward the null or limiting sample size such that the results were unlikely to be significant. Importantly, the small number of siblings within the final comparison created a lack of precision/stability and a lack of ability to detect statistically significant differences, which detracted from the study's validity. The within-family result (HR 1.06, 95%CI 0.51–2.05) demonstrates that the risk may have been as low as a 50% reduction in risk or as high as a 2-fold elevation.

Meta-analyses

Only one pooled study (Alemany 2021) and three meta-analyses (Masarwa 2018, Masarwa 2020, Ricci 2023) have been published summarizing the association between APAP use and ADHD. The Alemany (2021) analysis relied on behavioral measures and so is not included in my forest plot below. Instead, I considered it to contribute important context and review it as such below. Although the Masarwa papers also included studies that relied on behavioral measures, I have evaluated them in more detail given that the Court discussed them with some frequency.

Notably, the Masarwa authors published in 2018 and updated that result in 2020, adding a statistical analysis of confounding and bias. However, both Masarwa meta-analyses relied on some studies that assessed behavioral, non-diagnostic endpoints, rather than diagnostic endpoints. I include it in my assessment of Bradford Hill only because the Court's Order

discussed the Masarwa (2020) study, suggesting that the Court's Order relied in part on this study. I also reviewed Masarwa (2018) for context. But I underscore that the only meta-analysis with ADHD diagnosis as an outcome was Ricci (2023). The inclusion of Masarwa (2018) does not change the analysis. While the Masarwa (2018, 2020) metanalyses are not necessary to my opinions on strength and consistency, they are certainly consistent with those opinions.

Masarwa (2018 and 2020)

The Masarwa (2020) analysis was an update to the meta-analysis published by Masarwa in 2018. The authors combined seven eligible cohorts, involving 132,738 mother-child pairs, with follow-up periods ranging from 3 to 11 years. Six of these cohorts assessed ADHD-related outcomes, though not all diagnostic endpoints: Streissguth (1987), Brandlistuen (2013), Liew (2014), Thompson (2014), Avella-Garcia (2016), and Stergiakouli (2016). The remaining cohort, Liew (2016) assessed ASD-related outcomes.

A broad literature search was conducted for cohort studies and case-control studies, reporting hazard ratios, risk ratios, incidence rate ratios, odds ratios, mean differences, or regression coefficients for ADHD or ASD in the offspring of women exposed to APAP during pregnancy. Included studies were required to reach at least a 5-star level of quality in the Newcastle-Ottawa Scale (NOS). Random effects meta-regression analysis was used to combine study results.

The pooled risk ratio for ADHD was 1.34 (95% CI 1.21-1.47) and for hyperactivity symptoms it was 1.24 (95% CI 1.04–1.43). Conduct disorders were also elevated with prenatal APAP use (RR 1.23, 95% CI 1.04–1.42). The association between APAP exposure and ADHD was further explored by meta-regression analyses evaluating potential interaction effects. The impact of maternal APAP use increased with the child's age upon follow-up (β=0.03, 95% CI: 0.00–0.07), with the mean duration of exposure (β=0.00, 95% CI: 0.00–0.01), and with younger maternal

age (β=-.17, 95% CI: -0.28 to -0.60). Maternal fever, maternal smoking, high socioeconomic status, NOS score, and country latitude were not found to be significant confounders or effect modifiers. Sensitivity analyses involving exclusion of earlier studies had no impact on the results.

Notable in Masarwa (2018) are the Forest Plots showing the RR and CI of each study. Every study had a RR to the right of 1.0, with the exception of Brandlistuen (2013) for hyperactivity and for conduct disorder. However, Brandlistuen (2013) did show other (often statistically significant) effects from APAP on ADHD-related behaviors. This lack of heterogeneity was shown statistically, and the graphic consistency of the findings is striking. Meanwhile, with respect to any heterogeneity, the authors chose a random-effects model that took into account between-study variance and still found a statistically significant increase in risk. The authors also dealt with this heterogeneity by performing meta-regression analyses to rule out a number of potential confounders or effect modifiers. (Imrey 2020, Schroll 2011).

The same database was used in Masarwa (2020). Although the authors claimed that their endpoint was ADHD, this was NOT a diagnosis of ADHD. In fact, of the seven studies pooled (Streissguth 1987, Liew 2014, Ystrom 2017, Stergiakouli 2016, Avella-Garcia 2016, Thompson 2014, and Tovo-Rodrigos 2018), only Ystrom (2017) and Liew (2014) relied on a diagnostic outcome. Masarwa (2020) applied statistical tools to examine the potential for bias and confounding, employing quantitative bias analysis to estimate the direction, magnitude, and uncertainty arising from systematic error. Two scenarios were generated, one reflecting a higher participant probability among the mother-child pairs exposed to APAP and the other assuming the opposite. Both scenarios assumed non-differential selection. The assumptions in the selection bias models were that the probability of participation among exposed, with or without

an outcome, was assumed to be 85% whereas participation among unexposed, with or without an outcome was assumed to be 45%.

To evaluate the impact of exposure misclassification, the Masarwa (2020) authors again assumed non-differential misclassification since the probability of APAP exposure was unrelated to outcome. They modeled probability density functions for sensitivity of between 0.55 and 0.80 and specificity between 0.9 and 0.99. In other words, they assumed that between 55 and 80% of women would remember and report APAP use. Of those who reported use, 90 to 99% would be actual users.

The results of the updated Masarwa (2020) meta-analysis were that prenatal APAP use increased the odds of developing ADHD by 35% (RR 1.35, 95% CI 1.25–1.46). After selection bias correction, the result was a corrected RR of 1.31 (95% CI 0.91–1.71). In Masarwa (2018), the pooled risk ratio for ADHD hyperactivity symptoms was RR 1.24 (95% CI 1.04–1.43) and for conduct disorders was RR 1.23 (95% CI 1.04–1.42). Thus, the Masarwa (2020) updated analysis using the yes/no ADHD diagnosis as an outcome showed a slightly increased risk estimate as compared to the behavioral measures.

Masarwa (2020) states: “The sensitivity analysis plot for updated meta-analysis is shown in Figure 3. A bias factor of 1.50 (equivalent to a confounder, associated with both the exposure and outcome with a strength of RR = 1.69) was required to reduce the proportion of studies with a true RR > 1.10 to reduce the proportion of studies with a true RR of >1.10 to <10%. An E-value of 2.03 was required to explain away the significant association found in this meta-analysis.”

The Masarwa (2020) authors then go on to explain, “Meta-analysis of bias-corrected estimates resulted in a [bias corrected RR] of 1.31 (95% CI 0.91, 1.71) when correcting for selection bias and 1.91 (95% CI 0.04, 3.77) when correcting for exposure misclassification.”

They explain the meaning of the E-value in the Method section: “The E-value is the minimum strength of association on the RR scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain an exposure-outcome association.” (Masarwa 2020)

They also comment on the individual studies as follows. “The E-values for each individual study suggested that an unmeasured confounder as small as 1.61 in the study by Stergiakouli et al and 2.38 in the study by Liew et al would be required to explain the observed association. These results are compatible with reported strengths of the confounding associations for parental ADHD (OR 1.68) and maternal migraine (OR 1.81).” (Masarwa 2020) Of the seven studies included in this meta-analysis, only Liew (2014) and Ystrom (2017) had diagnostic endpoints so, it is relevant that a very large confounding effect would be needed to nullify the Liew (2014) result.

What does all of this mean in common English? I break this down into several points.
First, considering only confounding (without bias), a confounding factor would theoretically need to have a RR of 1.69 or greater to make the great majority of results go away. However, when applied to their own meta-analysis, the confounder would have to have a strength on the order of 2.03 to explain away their own significant result.

Second, the literature suggests that genetic confounding, as measured by the surrogate marker (parental ADHD), has a strength of association of 1.68. So parental confounding would be

almost large enough to theoretically make a result appear insignificant. But, in their own analysis, it would not eliminate their significant finding, because to do that, the strength of association for parental confounding would need to be 2.03.

Third, exposure misclassification bias correction increased, rather than decreased the observed effect sizes. Selection bias had little effect (bcRR of 1.31 (95% CI 0.91, 1.71)). But correction for exposure misclassification elevated the estimate to 1.91 (95% CI 0.04, 3.77). This later estimate was, notably, highly imprecise with a large confidence interval. But the Masarwa (2020) authors focus on the point estimates throughout their paper and note that the estimate is increased after bias correction. To quote from their Comment section: “Exposure misclassification QBA [quantitative bias analysis] increased the strength of the estimated association (bcRR 1.91, 95% CI 0.04, 3.77; I^2 = 0%) compared to that estimated in the updated meta-analysis. Although the observed association became non-significant, it strengthened, after assuming a range for sensitivity and specificity values for the reported use of analgesic medications during pregnancy. This may indicate under-reporting of OTC medications during pregnancy and that the observed association may be underestimated. In addition, the exposure definition was binary, with women classified as ever-users versus non-users, potentially resulting in substantial exposure misclassification.” In other words, the authors indicate that exposure misclassification was likely a large problem and that it artificially diminished observed associations.

Fourth, in Figure 3, Masarwa (2020) shows the impact of confounding and bias together and that the two counter each other. As bias increases, the strength of the confounding factor has to increase in order to maintain the same proportion of studies that become insignificant. Given their analyses, this is exactly what would be expected. A confounding of large magnitude (RR 2 to eliminate their own findings) would account for a spurious observed risk. But exposure misclassification would mute the observed risk. So, in aggregate, a very large confounding

effect would be needed to overcome the impact of exposure bias. None of the known potential confounders, particularly parental ADHD (RR 1.68), would be large enough to eliminate their own results and the factor would have to be even stronger to eliminate their own results after consideration of the countervailing effect of misclassification.

Masarwa Critique

Masarwa (2020) interpreted statistical analysis as indicating that bias explained the APAP and ADHD relationship. "Bias analysis suggests that the previously reported association between acetaminophen use during pregnancy and increased risk of ADHD in the offspring may be due to unmeasured confounding. Our ability to conclude a causal association is limited." (Masarwa 2020) "These results demonstrate that, under the assumptions made, selection bias resulting in a higher participation rate among a less or more healthy population does not explain the observed association. Exposure misclassification QBA increased the strength of the estimated association (bcRR 1.91, 95% CI 0.04, 3.77; 2 = I^2 = 0%) compared to that estimated in the updated meta-analysis. Although the observed association became non-significant, it strengthened, after assuming a range for sensitivity and specificity values for the reported use of analgesic medications during pregnancy. This may indicate under-reporting of OTC medications during pregnancy and that the observed association may be underestimated." (Masarwa 2020)

Masarwa (2020) also notes: "Under the assumptions of our bias analysis, we showed that unmeasured confounding and exposure misclassification bias play a role in this literature." "The observed association between acetaminophen use during pregnancy and the increased risk for ADHD in the offspring is likely the result of bias. This systematic error appears to be predominantly driven by unmeasured confounding and exposure misclassification." (Masarwa 2020)

My own assessment is this. The Masarwa (2018, 2020) database was large and heterogeneous. In the initial paper, adjustment was made for many relevant confounders and this follow-up additionally adjusted for potential bias. The initial paper found homogeneity of the findings among the different cohorts which, among statisticians, is a reason to not pool such data. This, then detracts from the validity of both the 2018 and 2020 result.

Other substantial limitations in the Masarwa (2018, 2020) analyses follow. First and most notably, both meta-analyses were based on studies that dominantly did not have diagnostic ADHD outcomes but instead used behavior outcomes.

Second, meta-analyses are only as good as the underlying studies on which they are based. Several of the studies included here were of lower quality. For instance, Thompson (2014), using data from the Aukland Birth Cohort (ABC), was a small study that only addressed exposure later in pregnancy and had high drop-out rates. Moreover, Thompson (2014) used an unusual and non-generalizable sample that over-represented babies with SGA. Avella-Garcia (2016) was also a relatively small study with low participation rates. Exposure to APAP was captured in the Spanish Birth Cohort, on which the analysis was based, using an open-ended question about medications which would have seriously underestimated true exposure and biased results towards the null. Streissguth (1987) was an early study of only 355 mother/child pairs. It was highly flawed, involving a highly selected, high socioeconomic group, and using an unvalidated instrument of attention. The authors considered their analysis “exploratory.” The original report did not include the outcome of ADHD – one can only guess that Masarwa (2018, 2020) translated the attention scores to a risk ratio. Although Masarwa (2018, 2020) included publications by Liew (2014), representing DNBC, it did not include publications arising from MOBA or ALSPAC or GESTE, or the Boston Birth Cohort, all of which have contributed large numbers, many publications, and more precise measurement techniques, to the APAP and

ADHD literature. Because the Masarwa (2018, 2020) meta-analyses were based on a selected group of studies of varying quality, its results must be viewed with caution.

Third, dose and amount of use were not harmonized across cohorts. Moreover, Masarwa (2020) did not address confounding by indication or genetics.

Finally, given loss to follow-up in the various studies included, selection bias could have impacted some of the results. Moreover, reliance on mostly smaller studies limited precision and the stability of estimates in individual results.

The original Masarwa (2018) meta-analysis examined the relationship between prenatal APAP use and symptoms of ADHD, ASD, hyperactivity, and conduct disorders over seven cohort studies, both separately and together. This allowed for a very large sample size to be analyzed and for inter-study consistency to be evaluated. (However, this total number mostly reflected counting the DNBC since other cohorts were small). The results revealed effect sizes of 1.19 to 1.34 for the various outcomes, all statistically significant. The consistency of results between studies was striking, particularly given the many design flaws in the underlying studies. However, the studies comprising the Masarwa database were markedly flawed, such that both the 2018 and 2020 results must be considered with caution.

Although after correction for misclassification, the RRs of 1.31 and 1.91 were no longer significant, this represents a loss of precision and power, not a diminution of the effect size – indeed the effect sizes were increased from the original Masarwa (2018) results.

Considering both the bias and confounding analyses, correction for exposure misclassification resulted in an increase in the adjusted RR of about 45%; correction for confounding resulted in

a maximum decrease of 19%. Thus, the two spurious effects were in opposite directions, with exposure misclassification having the greater impact, i.e., even after accounting for both, the result would be a greater bias toward the null.

Notably, Masarwa (2018, 2020) based their findings on hypothetical models that made a variety of assumptions. Those assumptions may or may not be accurate.

The fact that Masarwa (2018, 2020) here predominantly used behavioral outcomes and that the underlying studies had numerous flaws must be stressed in assessing the validity of this analysis. Because the studies on which Masarwa (2018, 2020) is based were so flawed, the results must be viewed with caution. Moreover, the lack of precision is a major limitation that makes the results difficult to interpret and detracts from validity. The conclusion that unmeasured confounding inflated other study estimates and thus explains the association between prenatal APAP use and ADHD is countered by Masarwa's (2018, 2020) finding that unmeasured bias deflated other study estimates.

Moreover, when applied to their own data, a confounder would have to be sizeable (RR 2.03) to nullify their meta-analytic result. Because they note that the size of the parental ADHD confounding effect was 1.68, parental confounding would NOT eliminate their result. In particular, in the Liew (2014) study—one of only two in the meta-analysis with a diagnostic endpoint—1.68 would not eliminate the effect. Thus, on the whole, it remains unlikely that either confounding or bias invalidates the other study results summarized here.

Ricci (2023)

In the most comprehensive meta-analysis to date and the only one with an analysis based on diagnosed ADHD as outcomes, Ricci searched the English language literature for studies of

acetaminophen and ADHD. These were rated on a standardized quality scale (Systematic Assessment of Quality in Observational Research) and pooled RRs were generated using random effects models.

Twenty-two studies including 23 cohorts met the authors' study criteria (n=367,775 total participants; median: 51.7% with APAP exposure). All but one study were prospective cohorts, most conducted in Europe and the US. The outcome of interest was ADHD, identified by a diagnosis, clinical evaluation, or caregiver self-report.

The Systematic Assessment of Quality in Observational Research (SAQOR) scale was used to rate study quality. SAQOR has the following domains: sample, comparison group, quality of exposure and outcome measures, distorting influences, and reporting of data. On the basis of these domains, studies were rated as having an overall quality score of high (5/5 domains rated as adequate), moderate (4/5), low (3/5), or very low quality (≤2/5). Using this instrument allowed the authors to evaluate the extent to which studies addressed confounding by indication (maternal fever and infection, inflammatory disorders, musculoskeletal or joint diseases, and pain) as well as the use of other analgesics. Of the studies reviewed, 13.6% rated as high, 59.1% as medium, 22.7% as low, and 4.5% as very low quality. As the Court noted, "[o]ne-third of the studies included in the review were rated as having low or very low quality based on concerns about caregiver self-report of exposures and outcomes." Order at 36. Elsewhere in this report, I extensively discuss the effect of using self-reported data. Studies rated as high quality were Anand (2021), Ji (2108) and Ji (2020), meeting all five SAQOR domains. Baker (2020), Liew (2019), and Ystrom (2017), among others, received a moderate quality rating, meeting four of five SAQOR domains. The studies with a diagnostic ADHD outcome (Ji (2020), Baker (2020), Liew (2019), and Ystrom (2017) (see Figure 3) are presented below and informative in my assessment.

The authors produced fully adjusted pooled RRs using random effects modeling when there were ≥ 3 studies with sufficiently homogeneous measures to pool. RRs were calculated (1) by the duration of APAP exposure (high, medium, or low, as defined by study authors); (2) by age at outcome assessment (≥6 years or<6 years of age); and (3) after exclusion of women with possible indications for APAP use (fever and infection, inflammatory disorders, musculoskeletal or joint diseases, or pain).

To assess residual confounding by indication, Ricci et al. calculated the strength of confounding needed to attenuate any observed associations. They then used a standard method (Grading of Recommendations, Assessment, Development and Evaluations or GRADE approach) to ascertain the overall certainty of evidence for the pooled results, either downgrading or upgrading studies based on methodology. Rationale for downgrading were methodological limitations as identified by SAQOR as follows: dissimilarity of research evidence (in terms of population, exposure, or outcomes), imprecision (95% confidence intervals including the null value, or a small sample size of<2000), inconsistency (differences in the magnitude of effects across studies), and the likelihood of publication bias (smaller studies contributing the positive values). Criteria for upgrading were a large effect size (RR>2.0), a dose–response relationship between exposure and outcome, and attenuation by plausible confounders.

Of the studies reviewed in Figure 3, together they studied 122,294 pregnant mother/child pairs. All were published between 2017 and 2020. In each about half of participants were male. The age at follow-up ranged from 6-11, except for Ystrom, in which outcomes were obtained at age 3. The weights given to the four studies were: Baker 16.3%, Ji 21.9%, Liew (2019) 28.6%, Ystrom 33.3%. Each of the individual studies reported a significant positive relationship between prenatal APAP use and ADHD, ranging from 1.12 to 2.25. The meta-analytic pooled risk

estimate, adjusting for maternal and infant characteristics was 1.47 (95% CI 1.12–1.92). Although there was some heterogeneity in the studies, the authors chose a random-effects model that took into account between-study variance and still found a statistically significant increase in risk. (Imrey 2020, Schroll 2011). Although the Court is correct that "the authors were not able to adjust for confounding by indication or parental ADHD in this analysis," Order at 35, the other analyses performed in the Ricci paper suggest (as the authors note) that confounding by indication is unlikely to be driving these associations. These analyses are explained in greater detail below.

This result was consistent with the overall pooled study result for ADHD (including behavioral outcomes) of a 32% elevated risk of ADHD (unadjusted pooled RR 1.32, 95% CI 1.20–1.44 n=7 studies). After adjusting for maternal and infant characteristics plus further adjusting for confounding by indication (for context, Avella-Garcia, Liew (2014), Stergiakouli, Ji (2020)) the pooled RR was 1.34 (95% CI 1.15–1.55) with "moderate to considerable" heterogeneity among study results. The fully adjusted pooled RR was strongest for the longest duration of exposure (pooled RR 1.84 95% CI 1.46–2.31) wherein there was limited heterogeneity. Age at assessment had little affected the pooled RR. Finally, when the authors excluded women with fever, the pooled RR remained elevated (pooled RR 1.61 95% CI 1.21–2.13), again with low study heterogeneity.

Assessing the potential impact of confounders, the authors show that for all indications, the confounder-exposure and confounder-outcome effect estimates would both have to be at least RR=3.00 or greater to explain the findings. Notably, the RR for fever (reviewed above) has been in the RR 1.2–1.4 range.

In e-figure 5, Ricci presents a bubble plot showing the impact of various adjustments and restrictions on effect estimates by individual study, colored by their quality. Green dots represent the highest quality studies. The plots show the vertical spread of RRs for unadjusted analyses, adjusted for covariates, adjusted for covariates plus indication, restricted to mothers without indications, and stratified by indications. After adjustment for indications, almost all the dots are above 1.0 with the highest above RR=3.0. After restriction such that only mothers without fever/infection are considered in the analysis, RRs for the relationship between APAP use and ADHD are uniformly 1.0 and green dots are all at the top. This demonstrates that in the analysis that most rigorously excluded confounding by indication, the best studies showed the highest risks and all studies showed positive associations with effect sizes ranging from >1.0 to >3.0.

Ricci e-tables also show the specificity of the ADHD effect. Studies examining developmental delays in domains such as cognition, motor, and language did not show substantial links to APAP use. However, diagnoses of ADHD consistently established the associations, with effect sizes >1.0 and often significant. Of the 13 results shown in e-Table 8, all 13 reported RRs >1.0 and 10 of 13 RRs were statistically significant.

Ricci Critique.

Ricci's summary of their results "indicated a small to moderate association between in utero acetaminophen exposure and risk of child ADHD, which did not appear to be explained by confounding by indication." "Prior studies in our review accounted for these indications via multivariable adjustment, restriction, stratification, sibling design, and negative control exposure." However, Ricci went beyond these analytic techniques to statistically assess the likelihood that indication bias affected the APAP and ADHD association: "The figure shows that

for all indications, the confounder-exposure and confounder-outcome effect estimates would have to be RR = 3.00 or greater to explain the findings."

Regarding dose response findings, they say, "In our meta-analysis, the strength of the association between in utero acetaminophen exposure and child ADHD was strongest in individuals with the highest duration of exposure, suggesting a dose–response effect."

They do, however, discuss the following limitations: "[T]he certainty of the evidence on this topic is low, and findings should be interpreted in light of the limitations of the existing studies, as well as the limited number of sufficiently comparable studies available to meta-analyses." They also note that confounding by indication could not be controlled for completely in every analysis, that parental ADHD had not been entirely controlled for, and that measurement error and confounding could have played a role in some of the results.

My assessment of Ricci is that there is much to commend in this meta-analysis. As the most recent study to pool the existing data, it is more comprehensive than any past attempt. Ricci and co-authors demonstrated the vastness of the literature on APAP and ADHD; they evaluated 22 studies including 23 cohorts and 367,775 total participants. (They excluded duplicative reports, including only the most recent analysis). The use of an accepted metric on which to base quality was a study strength.

Studies with the hard outcome of ADHD diagnosis were of moderate or high quality. Some of these assessments are worth commenting on. For instance, Baker, despite the use of meconium as a biomarker of exposure and physician diagnosis as a measure of outcomes, was assigned a quality score of moderate since it adjusted for a limited number of confounding factors. Two of the seven studies pooled by Masarwa (Avella-Garcia and Stergiakouli) were rated as low quality by Ricci.

Conservative statistical approaches were used to ensure that observed risks were not overestimated. Most importantly, the study assessed in detail the possibility that confounding by indication impacted the association between APAP use and ADHD (measured using a combination of diagnostic and behavioral measure) and showed that it did not.

The main limitation of the Ricci analysis is that because it was designed to consider confounding by indication (which it convincingly excluded as an explanation for the APAP-ADHD relationship) it did not specifically address genetic confounding.

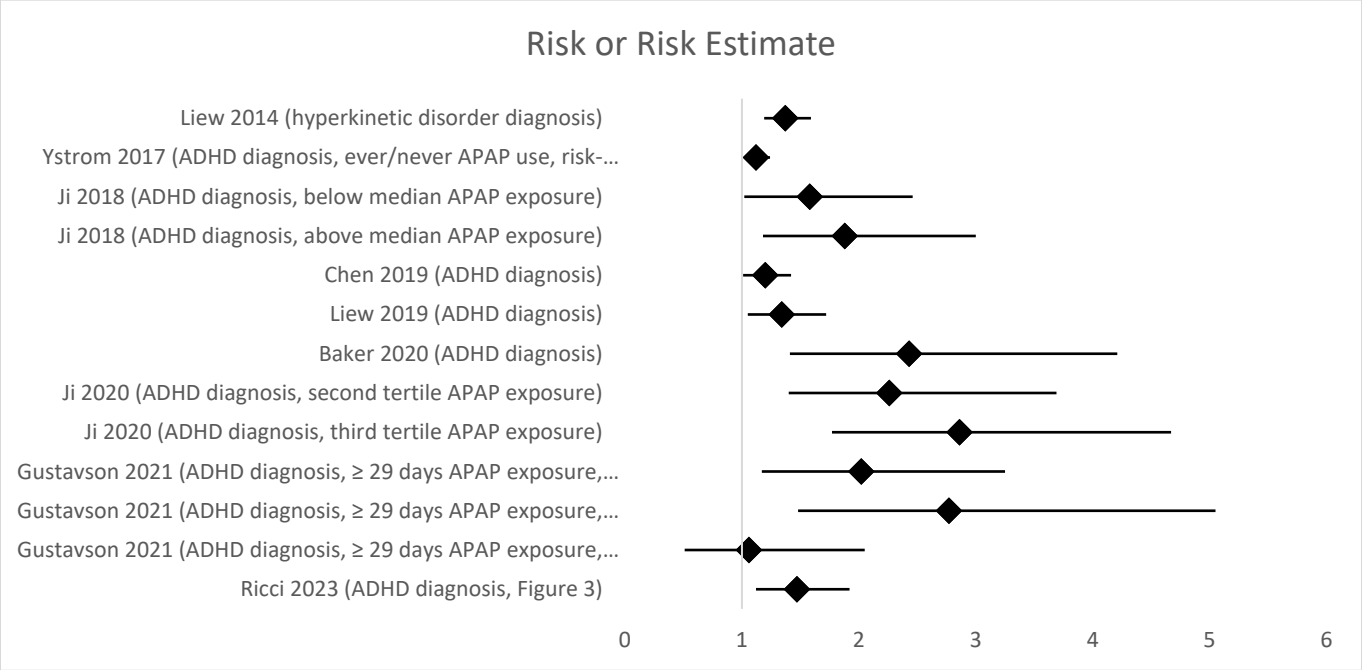
The results from the Ricci meta-analysis were in the same range as those from the Masarwa (2018) and Marsarwa (2020): 1.2 to 1.5. Those two meta-analyses relied on different datasets, adding power and certainty to the fact that the association is real. For the most exposed, the RR rose to 1.6. Also like the Masarwa meta-analyses, the Ricci Forest plot shows a remarkable consistency among studies in that all reported point estimates to the right of 1.0, i.e. a positive association. Further, after considering only mothers without APAP indications, the highest quality studies showed the highest RRs (as high as >3.0). Thus, Ricci contributes to a line of evidence showing that APAP use during pregnancy increases the risk of ADHD by 20 to 50% and more so in the highest exposure group.

Forest Plot of Studies with ADHD Diagnostic Outcomes

Below is a forest plot (and underlying data) of results of primary and aggregate analyses from nine studies with diagnostic outcomes: seven cohort studies (Liew (2014), Ystrom (2017), Ji (2018), Liew (2019), Baker (2020), Ji (2020), and Gustavson (2021)), one nested case-control study (Chen (2019)), and one metanalysis (Ricci (2023)). I reported the results of primary and aggregate analyses of each study because the larger sample sizes and higher statistical power

of those analyses allow detection of a statistically significant difference when one actually exists. I did not report the results of every subanalysis or stratified analysis in the forest plot because the smaller sample sizes and lower statistical power of those analyses may limit the utility and interpretation of those results.

Of note, the results of all primary and aggregate analyses except the within-family sibling-controlled analysis in Gustavson 2021 were statistically significant at 95% confidence, and even in that analysis the point estimate was elevated at 1.06.



Study	Risk or Risk Estimate	Lower 95% CI	Upper 95% CI
Liew 2014 (hyperkinetic disorder diagnosis)	1.37	1.19	1.59
Ystrom 2017 (ADHD diagnosis, ever/never APAP use, risk-adjusted Model 3)	1.12	1.02	1.24
Ji 2018 (ADHD diagnosis, below median APAP exposure)	1.58	1.02	2.46
Ji 2018 (ADHD diagnosis, above median APAP exposure)	1.88	1.18	3
Chen 2019 (ADHD diagnosis)	1.2	1.01	1.42
Liew 2019 (ADHD diagnosis)	1.34	1.05	1.72
Baker 2020 (ADHD diagnosis)	2.43	1.41	4.21
Ji 2020 (ADHD diagnosis, second tertile APAP exposure)	2.26	1.4	3.69
Ji 2020 (ADHD diagnosis, third tertile APAP exposure)	2.86	1.77	4.67
Gustavson 2021 (ADHD diagnosis, ≥ 29 days APAP exposure, risk-adjusted)	2.02	1.17	3.25
Gustavson 2021 (ADHD diagnosis, ≥ 29 days APAP exposure, between-family)	2.77	1.48	5.05
Gustavson 2021 (ADHD diagnosis, ≥ 29 days APAP exposure, within-family)	1.06	0.51	2.05
Ricci 2023 (ADHD diagnosis, Figure 3)	1.47	1.12	1.92

Bauer Consensus

Summarizing the literature up until 2021, Bauer et al. (2021) published a Consensus Statement in *Nature Reviews*, concluding: “We recommend that pregnant women should be cautioned at the beginning of pregnancy to: forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long-term basis; and minimize exposure by using the lowest effective dose for the shortest possible time.” (Bauer 2021, p 757) Signed by 91 of the world’s top epidemiologists and reproductive scientists, its precautionary warning was based on a comprehensive review. The review did not distinguish between ADHD and ASD as outcomes. Combining the two, the authors pointed to 29 observational studies in 14 cohorts, including over 220,000 mother–child pairs from different parts of the world. Fully 26 of the 29 studies yielded positive associations between APAP use during pregnancy and neurodevelopmental outcomes. Of 21 studies that specifically looked at ADHD or ASD or both, 18 found a positive link to prenatal APAP exposure.

Moreover, by the authors’ count, dose (duration or concentration) of APAP use during pregnancy was evaluated in 19 studies,16 of which revealed a positive association. It appears that the highest risk period may be the second and third trimesters.

With respect to confounding, Bauer notes the many methods used to exclude confounding, particularly confounding by indication and by genetics, as causes of a false exposure-outcome relationship. With respect to the former, Bauer points out that many of the studies adjusted or stratified for APAP indications and still found associations. Moreover, neurodevelopmental outcome risks were consistent across indications. They note that different indications are unlikely mechanistically to affect disease risk in similar ways. This argues against confounding by indication. With respect to familial aggregation, 16 studies used a sibling control design,

polygenic risk scores, or negative controls. Fourteen of these 16, the authors say, have yielded a positive association between *in utero* APAP exposure and neurodevelopmental outcomes.

Bauer concedes that APAP is an important medication of high fever and severe pain but at the same time finds that "increasing experimental and epidemiological research suggests that prenatal exposure to APAP might alter fetal development, which could increase the risks of some neurodevelopmental, reproductive and urogenital disorders." (Bauer 2021, p 757) The authors then "summarize this evidence and call for precautionary action through a focused research effort and by increasing awareness among health professionals and pregnant women."

As noted above, several professional societies disagreed with Bauer's conclusions. In addition, two sets of researchers published their own counterstatements. In Alwan (2022), the authors and signatories stated their view that the relevant studies were "limited by serious methodological problems, including failure to account for confounding, and elements of bias that make interpretation of the data challenging." Although they agreed that "questions related to the safety of APAP use should continue to be investigated," they argued that "premature precautionary statements" could lead to undertreatment of maternal illnesses due to medication hesitancy." Similarly, in O'Sullivan (2022), a group of researchers again emphasized a "risk-benefit calculation, which should consider both the mother and fetus during pregnancy." In part for this reason, they argued that the current evidence did not warrant a change in clinical practice. Critically, neither of these responses to the Consensus Statement explained why they believed that something *other than* causation was the most likely explanation for the repeatedly observed associations between prenatal APAP exposure and ADHD. And neither performed a Bradford Hill analysis, as I have here.

Bauer replied to the concerns raised by the Alwan authors, saying, “We agree that limitations and uncertainties remain despite the large body of available data, therefore, we avoided any inference of causality in our Consensus Statement. We believe, however, that available data provide sufficient evidence for concern and a recommendation of precautionary action. The availability of a large body of experimental data, largely consistent with observational data, is an important consideration in our evaluation. Ethical considerations rule out clinical intervention trials for APAP in pregnancy, so animal studies, which are not subject to confounding or bias, are an essential source of evidence and support for causality.” (Bauer 2022) Their consensus statement was not a formal assessment of Hill’s tenets. Thus, like so many other authors, they were not in a position to comment on causality. Interestingly, they do comment that animal studies provide support for causality. Although not a review based on Hill criteria, and although it was published before the Ricci (2023) meta-analysis, the Bauer study represents one of the most comprehensive systematic reviews of the literature on APAP and adverse neurodevelopmental outcomes to date.

Other studies relevant to the question of APAP and ADHD that are important for context

Brandlistuen (2013)

In a secondary data analysis of the Norwegian Mother, Father and Child Cohort Study (MOBA), the authors used data from 1999 to 2008 involving 48,631 child-mother pairs who had completed a questionnaire when the child was age 3. The authors analyzed 2,919 same-sex sibling pairs in that group. Follow-up of the cohort involved questionnaires at pregnancy week 17, week 30, 6 months post-partum and 3 years.

APAP exposure was queried in any woman reporting headache, fever, cold, or backache. Among such women, medication use was asked in an open-text format. Timing and duration

were also ascertained, along with timing of use (6 months pre-pregnancy (baseline); gestational age (0–4, 5–8, 9–12, 13+ weeks (first follow-up), 13–16, 17–20, 21–24, 25–28 and 29+ (second follow-up), and week 30 until delivery (third follow-up));and duration of use, according to specific indication (e.g., “back pain,” “pelvic girdle pain,” and “headache”).

Almost 50% (46.1%) of women reported APAP use and 3.8% reported use for over 28 days duration (134 sibling pair mothers).

Using the validated “Ages and Stages” questionnaire, and the popular “Child Behavioral Checklist” questionnaire, functional outcomes of interest were considered. These included psychomotor behaviors, communication, fine and gross motor skills, externalization behaviors, internalization behaviors, behavior problems, temperament, emotionality, hyperactivity, sociability, and shyness.

Brandlistuen controlled a large number of potential confounders. These included: (1) indications for APAP use: infections, fever, back pain, headache/migraine; (2) other medication use: non-steroidal anti-inflammatory medications, benzodiazepines, anti-depressants, anti-psychotics, anti-epileptics; (3) maternal diseases: anxiety depression, chronic illnesses; maternal demographics, (4) lifestyle: age, parity, smoking, alcohol use, education, (5) characteristics of the siblings of interest: child sex, child malformations, gestational ages at birth, birthweights, sibling order, and (6) years between pregnancies. Regression models were adjusted for these variables.

Results of the study showed that within the 2,919 same-sex sibling pairs, children exposed as compared to unexposed to APAP *in utero* for >28 days had poorer behaviors in the areas of gross motor skills (β 0,24, significant), communication (β 0.20 significant), externalizing (0.28

significant), and internalizing (β .014 significant). Their mothers also reported increased activity (β 0.24 significant). To contextualize these differences (all reported as continuous variables), β of 0.28 translated into a RR of 1.69; β of 0.20 translated into a RR of 1.51. The adverse behaviors in children of mothers with longer-duration use during pregnancy were thus dominantly on the order of 50 to 70% increases in risk. Among women with shorter duration APAP use, gross motor skills were impaired (β 0.10 significant) but no other significant effects were found. These behavioral impacts were independent of trimester of use. Ibuprofen use was associated with no differences between sibling pairs.

Brandlistuen Critique.

This was a study with many strengths. It was large and had over 2,000 pairs even after including only same-sex siblings, allowing for 134 pairs whose mothers had used APAP for 28 days or more. As a cohort study, it ensured that exposure captured more than once during pregnancy would have preceded outcomes. A sibling-pair design was used to limit confounding by genetics/familial aggregation. Covariates for confounding by indication and other potential confounders were adjusted for in models. Follow-up was not long enough to capture adverse outcomes among children who later demonstrated symptoms consistent with the diagnosis of ADHD.

Weaknesses are that all outcomes were based on parental report. To the degree that this was the first cohort study linking APAP use to ADHD behaviors, it was unlikely, although not impossible, that mothers who had used APAP would have been more likely to report problems than non-users. Misclassification would thus have been non-differential and toward the null.

High drop-out rates are a concern within all MOBA analyses. This was not fully addressed in the Brandlistuen analysis, but it was in a later Vlenterie study. Long-term APAP users were

somewhat more likely to drop out (4.2% vs 3.7%). Although quite similar to non-dropouts, women who left the study had slightly higher depression rates, and more often were “not married or cohabiting.” As discussed above, bias in this situation would have been to underestimate true effect. Women using long-term APAP had healthier behaviors and their children would have tended to have less ADHD.

Exposure misclassification of APAP use was limited by focusing on long-duration users who probably would have less likely forgotten use. It was also limited by connecting the question on analgesics to indications for analgesic use. However, exposure misclassification may still have occurred, particularly because the question was open text around any medication use in situations of fever/pain.

Unadjusted confounding must be considered in any epidemiologic study, no matter how excellent the design. Finally, as noted above, use of siblings as controls, although going far to limit confounding by family aggregation, did not exclude it.

Overall, Brandlistuen was a study of relatively high quality and showed a plethora of significant effects on the order of 50 to 70% increases in adverse behaviors that have been linked to ADHD. The fact that longer duration users demonstrated these effects while shorter duration users did not argue for a dose-response, which is one of Hill’s tenets for causality.

Thompson (2014)

Thompson (2014) utilized the Aukland Birth Cohort (ABC). ABC enrolled 871 infants of European descent, disproportionately sampling infants born small-for-gestational age. Neonates and their mothers were ascertained between October 1995 and November 1997 from the Auckland District Health Board, and the Waitemata District Health Board. All small-for-

gestational-age infants and a random selection of appropriate-for-gestational-age infants were selected during the study, such that the number in each group were approximately equal.

Follow-up questionnaires were conducted at birth, and when children were 12 months, 3.5 years, 7 years, and 11 years old. Among European mothers (other ethnic group's follow-up was too poor to report results), respondents were more likely than non-respondents to have a tertiary education ($p = 0.05$), to be married ($p < 0.0001$), to have high socio-economic status ($p < 0.0001$), to not have smoked during pregnancy ($p < 0.0001$), and to be older ($p = 0.0001$).

Medication exposures were queried directly for APAP, aspirin, antacids, and antibiotics with the question, "did you use any of these?" Almost half (49.8%) of mothers reported use of APAP during pregnancy.

Neurodevelopmental measures were scored by parents when the child was age 7 on the Strengths and Differences Questionnaire (SDQ). Mothers or main caregivers were asked 25 questions about their 7-year-old child's behavior during the previous 6 months. As recommended for scoring of the SDQ, the authors created a total difficulties score (range, 0-40) by summing 4 subscales (emotional symptoms, con duct problems, hyperactivity, and peer problems), ranging from 0 to 10 each, with higher scores indicating an increasing number of behavioral problems, and omitting the prosocial behavior subscale (range, 0-10), for which higher scores indicate positive social behaviors. The same measures were reported by both parents and children when offspring were age 11. The SDQ measures ADHD-associated behaviors along five different axes with subscales of: conduct, emotion, hyperactivity/inattention, peer group relations, and pro-social. The validated Connors Behavioral Rating Scale long format (Connors) was further used to measure ADHD-associated behaviors.

The authors adjusted for maternal body mass index (BMI), education, socioeconomic status, smoking, marital status, stress, depression/anxiety, and fever during pregnancy. Also adjusted in models were child birthweight, sex, and small-for-gestational age.

After adjustment, the study found significant increases on the Connors scale among children at ages 7 and 11 by parental report. Significant increases among APAP exposed versus unexposed children were reported overall and in the attention and emotional lability subscales. On the SDQ, parents of children age 7 and 11 reported significantly increased scores overall and in the emotional lability area. Eleven-year-old children themselves reported increases on the SDQ in total score, and in the conduct problems and hyperactivity areas. None of the behavioral outcomes differed with use of any other medication including other analgesics.

Liew et al. (2014)

This study was included above but also had a behavioral endpoint. As such only that aspect of the study will be reviewed here.

ADHD-like behaviors were assessed on the standardized SDQ and its five domains of emotional symptoms, conduct problems, hyperactivity, peer relationships, and prosocial behavior in children and adolescents ages 4 to 16 years. Mothers or main caregivers were asked 25 questions about their 7-year-old child's behavior during the previous 6 months. As recommended for scoring of the SDQ, the authors created a total difficulties score (range, 0-40) by summing 4 subscales (emotional symptoms, con duct problems, hyperactivity, and peer problems), ranging from 0 to 10 each, with higher scores indicating an increasing number of behavioral problems, and omitting the prosocial behavior subscale (range, 0-10), for which higher scores indicate positive social behaviors. Parents also answered 6 questions (possible

value of 0, 1, or 2 for each) about their own behavioral problems during childhood, allowing for to generation of a parental behavioral problems score (range, 0-12) of ADHD-like symptoms.

Many confounding factors were included in the analyses, including maternal age, parity, socioeconomic status, smoking, alcohol use, BMI, psychiatric illnesses, diagnosed anxiety/depression, maternal childhood psychiatric disorder, maternal family problems/life crisis, and maternal childhood behavior problems. As well, indications for analgesic use such as fever, inflammation/infection, and diseases of muscles/joints were queried, as were use of aspirin and non-steroidal medications, folic acid, antibiotics, sleep medicines, and anti-depressants. Children's sex and year of birth were adjusted in models. Other potential confounders considered were father's age at the child's birth, Apgar scores, and season of conception. Only 5% of subjects had missing covariates.

Follow-up to the time of the Liew publication was an average of 12.7 years. The mean age of children at the end of follow-up was 10.7 years for hyperkinetic diagnoses and 11.2 years for ADHD medications.

More than half of all mothers reported acetaminophen use while pregnant. The authors observed an increased risk for ADHD-like behaviors in children at age 7 after maternal APAP use during pregnancy: Children whose mothers used APAP during pregnancy were at higher risk of having a high score for ADHD-like behaviors on the SDQ at age 7 (RR 1.13; 95% CI, 1.01–1.27).

Risk increased for use in more than one pregnancy trimester, especially in later pregnancy, and the authors observed a stepwise increase in risks for a higher SDQ overall score with increasing frequency of use throughout pregnancy. That is, in linear regression models, each additional

week of prenatal APAP use during pregnancy was associated with a higher SDQ behavioral score ($p<0.001$).

Moreover, for SDQ total symptoms, use in the second and third trimesters increased risk more than use in the first.

Liew Critique. Many of the strengths mentioned for MOBA apply to this secondary analysis of data from DNBC. The study was large, which allows for excellent precision around estimates. As a cohort study, it ensured that exposure captured more than once during pregnancy would have preceded outcomes. The cohort was population-based although response rates were not high (60%), meaning that selection bias and selective misclassification of exposure were not as limited as in MOBA. However, because two of three outcome measures were from registry data, the selection bias from missing telephone interview data for these was limited. Potential confounding was limited by inclusion of a large number of covariates in mothers, fathers, and offspring. However, genetic confounding was not considered. Validated questionnaires or use of hospitals and pharmacy registries promoted the validity and reliability of data. Moreover, ascertainment of exposure data at each of the second and third trimesters allowed for assessment of intra-reporter consistency and of duration of use. Follow-up was long enough to capture many of the signs and symptoms associated with ADHD, since that diagnosis is typically made by the pre-teen years.

Weaknesses included parental report of ADHD symptoms in the behavior analyses. It is unlikely, although not impossible, that mothers who had used APAP would have been more likely to report problems than non-users. Misclassification would probably, thus, have been non-differential. For ADHD and medication use, cases might have needed to have more severe forms of illness to seek medical attention and receive a diagnosis.

Exposure misclassification of APAP use was limited by use of a checklist of analgesics by name and by ascertainment of analgesic information at three time points during and shortly after pregnancy.

Unadjusted confounding must be considered in any epidemiologic study, no matter how excellent the design. In particular, limited adjustment was conducted around children's characteristics both at birth (e.g., birthweight) and during childhood (e.g., other medication use).

Overall, Liew was a study of high quality and showed a plethora of significant effects, with effect sizes on the order of 50 to 80% for ADHD symptoms among long-duration users. The fact that longer duration users demonstrated higher risks argues for a dose-response. Moreover, the study identified later pregnancy use as a sensitive window with risk of ADHD symptoms of 1.44.

Stergiakouli (2016).

This report was based on data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based prospective birth cohort. The authors studied 7,796 mothers enrolled in ALSPAC between 1991 and 1992 along with their children and partners. ALSPAC is a birth cohort in which 14,150 women residing in Avon, UK were enrolled at 18 weeks gestation and queried at 18 and 32 weeks regarding exposures during pregnancy. In this analysis, the authors assessed the relationship between prenatal APAP exposure and ADHD. Fully 88% of women responded. Mailed questionnaires specifically asked, "Please indicate how often you have taken the following pills in the last three months. (a) Aspirin; (b) Paracetamol; (c) Codeine; (d) Mogadon or other sleeping tablets; (e) Valium or other tranquilizers." Outcomes were maternal reports (6,300) and teacher reports (4,400) of ODD and CD symptom scores at age 7 years using the Development and Well-Being Assessment interview.

Exposures were recorded on questionnaires completed at 18 and 32 weeks of pregnancy and when the child was 61 months old.

Maternal reports of behavioral problems using the SDQ when the children were 7 years old. Standard cut-offs were used to identify high scores, as these have been validated in previous literature. Risks were calculated for behavioral problems in children after prenatal, postnatal, and partner's exposure to acetaminophen. RR estimates for prenatal exposure were mutually adjusted for postnatal and partner use.

Multiple potential confounding variables were included in models as covariates. These were selected by the authors as the most likely to lead to confounding by indication. Adjustments were made for pregnancy behaviors, including: maternal age at birth, parity, socioeconomic status, smoking and alcohol consumption, pre-pregnancy BMI, maternal self-reported psychiatric illness, joint problems, infections (including cold or flu, urinary, or other infections), migraine, or headaches.

Composite scores of molecular genetic risk factors for ADHD (polygenic risk scores) were calculated for 8,340 ALSPAC mothers using available genotype data using strict quality control protocols and standard internationally accepted methods. Polygenic risk scores were computed using "risk alleles" based on the results of an independent case-control United Kingdom/Ireland ADHD genome-wide association study (GWAS) (discovery sample). In line with previous studies, a threshold of P< .50 was used to select alleles more common in cases than controls from the discovery sample (single-nucleotide polymorphisms [SNPs] in relative linkage

equilibrium in the discovery sample GWAS were selected first). These identified SNPs were used to calculate a polygenic score for each individual in ALSPAC, corresponding to the mean number of score alleles (weighted by the logarithm of the odds ratio) across the set of SNPs.

Maternal prenatal acetaminophen use at 32 weeks of pregnancy (n = 3381; 42% APAP users) was associated with higher risk of having a statistical significantly high SDQ difficulty score (RR 1.46, 95% CI 1.21–1.77), emotional problem score (RR 1.29, 95% CI 1.09–1.53), conduct problem score (RR 1.42, 95% CI 1.25–1.62) and hyperactivity symptom score (RR 1.31, 95% CI 1.16–1.49). Smaller increases were seen for maternal APAP use at 18 weeks (4415 mothers; 53% APAP users). At that time point, statistically significant elevations were observed for conduct problems (RR 1.20, 95% CI 1.06–1.37) and hyperactivity (RR 1.23, 95% CI 1.08–1.39). Risks were not elevated for maternal postnatal APAP use (n = 6916; 89% APAP use) or partner's APAP use (n = 3454; 84% APAP use). The authors found the associations between maternal prenatal acetaminophen use and all the SDQ domains unchanged even after adjusting for maternal postnatal or partner's APAP exposure.

There was little evidence of association between maternal ADHD polygenic risk scores and maternal prenatal APAP use at 18 weeks of pregnancy (OR per SD of polygenic risk score, 0.99, 95% CI, 0.95–1.05; P = .90), 32 weeks of pregnancy (OR per SD of polygenic risk score 0.98, 95% CI, 0.94–1.03; P = .48), or with postnatal acetaminophen use (OR per SD of polygenic risk score 0.92, 95% CI, 0.85–1.00; P = .06). That is, there was no indication that the genetic risk score confounded the associations.

All analyses relating maternal prenatal APAP use and SDQ domains were repeated with potential confounders including the genetic risk score and the results were similar.

Stergiakouli critique.

The Stergiakouli report has a number of strengths. Most notably the polygenetic risk scores were a direct test of whether a biologic measure of genetic confounding influenced the APAP-ADHD association. It did not. Use of negative controls (NCE) to detect suspected and unsuspected confounding was another strength. NCE uses variable(s) that do not causally affect the outcome but share a similar confounding structure with the exposure variable of interest. Here, the authors compared risks from maternal prenatal exposure to those from paternal and maternal postnatal exposure and found the risks to be specific to prenatal APAP use. This suggests that confounding by genetics and other unmeasured confounders is not driving the prenatal association. Moreover, a strength of ALSPAC is that, like DNBC and MOBA, ALSPAC was a population-wide cohort study, representing substantial generalizability to women (at least in one county) in the UK.

Limitations of this analysis were as follows. Reliance on an ever/never categorization for APAP would have underestimated exposure. Moreover, it would have admixed long and short-duration users. Both the single time point and the lack of specificity on timing and duration of use would have biased results toward the null. A further consideration is that outcomes were based on self-report by mothers and on subjective scales. There is inherent bias in all studies based on psychological scales. In the case of these measures, children can be “labeled” as disruptive and it can be difficult to shed this perception. Again, any misclassification would have been non-differential and biased results toward the null, in that this would not have been related to knowledge of maternal APAP exposure. Another limitation was the somewhat limited duration of follow-up to age 7. Children developing ADHD symptoms after that point would not have been captured in this design. Neither fever nor maternal co-morbidities nor other medication use were included as adjustment factors, leading to a potential for unmeasured confounding, particularly confounding by indication.

In general, Stergiakouli had strengths but also weaknesses. Nonetheless, the use of both a genetic risk score and NCEs lends credibility to a lack of confounding by genetics. For later pregnancy use of APAP, risks for high levels of ADHD symptoms were increased on the order of 26% to 49%. Like several other studies, later pregnancy use was more strongly related to ADHD risk than earlier use.

Liew (2016)

Once again using data from DNBC, Liew analyzed 1,491 mothers and children in evaluating the association between prenatal APAP use and childhood attention and executive function at age 5.

The methodologies reviewed above for other Liew studies are the same here for the cohort overall. The current analysis was based on a sub-study conducted within DNBC called the Lifestyle During Pregnancy study (LDPS). LDPS was designed to study the relationships between prenatal lifestyle factors, primarily maternal alcohol intake and neuropsychological outcomes in children. From DNBC, 3,478 mothers and children were invited to participate in a 3-hour neuropsychological assessment conducted by trained psychologists when the children reached 5 years of age. Ten psychological testers, masked as to exposure status, administered the tests. All testing procedures were standardized, and inter-rater differences were minimal. Among those invited to participate, 1,782 (51%) agreed, but 291 women did not complete all interviews. Thus, the final sample included 1,491 mothers.

Outcomes of interest (i.e., attention and executive function) were ascertained in interviews by trained psychologists. Children's attention was measured using the Test of Everyday Attention for Children at Five (TEACh-5). Parents and preschool teachers completed the Behavior Rating

Inventory of Executive Function (BRIEF) to assess executive function. Analyses estimated the differences of composite mean outcome scores and produced ORs for subnormal attention or executive function (defined as 1 standard deviation below the mean), adjusting for maternal IQ, maternal mental health, indications for paracetamol use and other potential confounders (as noted for other Liew analyses).

Children born to mothers who used APAP during pregnancy performed more poorly on tests for overall attention (mean difference -0.10, 95% CI -0.26–0.05) and selective attention (mean difference -0.12, 95% CI -0.28–0.04) compared with the unexposed. These effect estimates were larger when acetaminophen was used in the first trimester (mean difference -0.34, 95% CI -0.63, -0.05 for overall attention, and -0.25, 95% CI -0.50–0.01 for selective attention). At the same time, third trimester differences in executive function were larger than first trimester differences (-1.24, 95% CI 3.52–1.04 third vs. -0.58, 95% CI -1.52–2.68). In terms of categorical risk among children who performed one standard deviation below the mean, those exposed to APAP in utero showed significantly elevated risks of subnormal overall attention (OR 1.5, 95% CI 1.0–2.5), selective attention difficulties (OR 1.5, 95% CI 1.0–2.4), and parent-rated subnormal executive function (metacognition index, OR 1.5, 95% CI 0.9–2.3). These elevated risks were similar in the first and third trimesters. With more trimesters of use, risk for problems in overall attention increased. RRs were 1.03 (95% CI 0.82–1.29), 1.25 (95% CI 0.95–1.65) and 1.16 (95% CI 0.94–1.42) for the first, second, and third trimesters, with a statistically positive test of trend (the overlapping confidence intervals for 1.25 and 1.16 indicating no statistical difference between these estimates). Dose-response trends were not seen for other outcomes.

Risks among boys and girls were similar for attention but parents reported more executive function problems in exposed boys. Limiting the analyses to mothers who never reported fever

or never reported infection/inflammation or never had musculoskeletal diseases had little impact on the results.

Liew critique. For brevity, I will not repeat the list of strengths and weaknesses addressed for Liew (2014). The new element here was the use of validated measures of attention and executive function at age 5. A strength of the method used to capture attention metrics was employment of trained psychologists reliably using validated measurement instruments. For executive function measures the availability of both parental and teacher responses was another strength.

A weakness with respect to the outcome measures was the relatively low participation rate in LDPS. The authors do not report characteristics of participants versus non-participants so it is unclear what biases this would have introduced.

Overall, Liew was a study that showed significant effects in attention and elevated (albeit non-significant) effects in executive function. This contributed another dimension to the now-building body of evidence that prenatal APAP use is associated with behaviors in the ADHD spectrum. Risks for attention and executive function at age 5 with use of APAP were 50% higher among exposed versus unexposed. Longer duration use appeared to impart greater attention-related risks.

Avella-Garcia (2016)

This analysis used data from the Spanish birth cohort. Included were 2,644 mother-child pairs recruited during pregnancy. Recruitment rates were in the 60% range, but follow-up was high with 88.8% of children evaluated at one year and 79.9% evaluated at 5 years.

Data were collected prospectively by interviewing expectant mothers at weeks 12 and 32 of pregnancy using standardized questionnaires administered by trained evaluators. APAP use was obtained by asking the question “Have you taken any medication (sporadically or continuously) since 1 month before becoming pregnant or during this pregnancy?” If the answer was positive, the name of the medication, dose, duration, gestational age at use and the indication as reported by the mother were asked using open questions. At week 32, mothers were asked about use of medication after week 12. Data were coded by a pharmacologist. APAP was categorized in various analyses as ever/never use and frequency of use (never, sporadic, persistent).

Main neurodevelopment outcomes associated with ADHD symptom scores were assessed using Conner’s Kiddie Continuous Performance Test (K-CPT). This standardized scale has been shown to identify inattention and hyperactivity/impulsivity symptoms as well in younger children (ages 2 to 5 years of age) as they do in older children. K-CPT is a computerized test that evaluates ADHD-related behaviors including attention function, reaction time, accuracy, and impulse control. Measures on K-CPT include: commission errors in which a target stimulus is presented but the child fails to respond to it; commission errors in which the child responds to a non-target stimulus; HRT-SE (Hit Reaction Time Standard Error) which corresponds to the variation in time of latency before a response; and detectability which shows the capacity to distinguish target from non-target stimuli. These K-CPT variables have all been correlated to ADHD symptoms.

Regression models were adjusted for social determinants and co-morbidities. These included: residence by region of Spain, child gender, age at testing, gestational age at birth, quality of test as rated by the performing psychologist, maternal social class, IQ, education and whether the mother reported having any chronic illness, fever or urinary tract infection-not necessarily

related to acetaminophen use-during pregnancy; and, for outcomes at 1 year of age, additional adjustment was made for prematurity.

Over 40% of mothers reported using APAP. After adjustment for confounders, ever-exposed offspring had higher risks of presenting more hyperactivity/impulsivity symptoms on the ADHD scale (RR 1.41, 95% CI 1.01–1.98), K-CPT commission errors (RR 1.10 1.03–1.17), and lower detectability scores (β 0.75, 95% CI 0.13–0.02). CAST scores were increased in ever-exposed boys (β 0.63, 95% CI 0.09–1.18).

Effect sizes increased among more frequent users for hyperactivity/impulsivity symptoms (RR 2.01, 0.95–4.24) in all children, for K-CPT commission errors and (RR 1.32, 1.05–1.66) detectability in girls, and CAST scores in boys (β 1.91, 0.44–1.38). Trends showing increased frequency of APAP use linked to attention were significant.

Stratification by indication for APAP use had no substantial effect on estimates.

Avella-Garcia Critique. Strengths of the Spanish birth cohort are its longitudinal design and national scope. It had high follow-up rates, increasing validity. Pregnant women were recruited early in pregnancy (12 weeks) and follow-up was until 5 years of age when, according to the authors, they could reliably and validly assess ADHD symptoms. A number of potential confounding factors were adjusted. Outcome measures were obtained based on validated, standardized tests administered by trained interviewers.

Weaknesses are several. The study was of modest size so that estimates were not precise. Relatively low participation rates raise the possibility of selection bias. Exposure to APAP was captured using an open-ended question about medications. This almost surely underestimated

use. About 40% of women reported APAP use but as noted above, at least in the U.S., prevalence of use is more like two thirds. This bias would lead to underestimating the true effect. A further weakness in the exposure measure was the categorization into ever/never use and a crude estimate of frequency of use (never, sporadic, persistent). The authors did not present data by trimester of use and did not have data on duration. Frequency would have crudely given some indication of dose but users could have been persistent for short periods.

Although the list of confounders was substantial, it did not capture a number of those adjusted in the Scandinavian studies, particularly maternal co-morbidity, and familial aggregation. The authors did, however, specifically stratify by indications for APAP use.

Overall, the Avella-Garcia study had limitations. Nonetheless, it showed adverse effects on attention-related outcomes for both genders. These associations were stronger among mothers who were more frequent APAP users during pregnancy. Among more frequent users, risks were elevated 40% to 220%.

Ruisch (2018)

Ruisch used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a birth cohort in which 14,150 women residing in Avon, UK were enrolled and queried at 18 and 32 weeks regarding exposures during pregnancy to assess the link between prenatal risk factors, including APAP, and oppositional defiant disorder (ODD) and conduct disorder (CD) symptoms. Fully 88% of women responded. Mailed questionnaires specifically asked, “Please indicate how often you have taken the following pills in the last three months. (a) Aspirin; (b) Paracetamol; (c) Codeine; (d) Mogadon or other sleeping tablets; (e) Valium or other tranquilizers.” Outcomes were maternal reports (6,300) and teacher reports (4,400) of ODD and CD symptom scores at age 7 years using the Development and Well-Being Assessment interview.

Control variables included comorbid attention-deficit/hyperactivity disorder symptoms, ODD or CD symptoms as appropriate, and genetic risk scores based on an aggregation of allelic variants found to be related to CD in a genome-wide association study. Moreover, analyses adjusted for socio-demographics, maternal age, smoking, alcohol consumption, cannabis and hard drug use, medications for infections and for anxiety or depression, maternal infections, anxiety, depression, life stressors, low birth weight, and preterm birth.

When adjusted for all other included pregnancy factors in the multivariable models, as well as comorbid OCC or CD scores plus genetic factors, maternal APAP use (P=0.015 for teacher ratings) and life events stress scores (P=0.004 for maternal ratings) were significant predictors of higher ODD symptom scores whereas maternal smoking (maternal ratings P<0.001), life event scores (maternal scores P<0.001), and depression scores (P=0.008 for teacher scores) were significant predictors of higher CD symptom scores. In other words, APAP use significantly predicted continuous scores of ODD symptoms but not CD symptoms.

Translating this into relative risks, higher ODD symptom scores were linked to APAP use (IRR=1.24, 98.3% CI 1.05–1.47), a finding that correlated highly with teacher ratings (P=0.002). As noted above, after adjustment for genetic score, the link between APAP exposure and ODD remained significant.

Ruisch Critique

ODD and CD are not subsets of ADHD, yet their symptoms overlap. ODD is the most common comorbidity diagnosed with ADHD. It is estimated that about 40% of children with ADHD also have ODD. ODD and CD are strongly associated with hyperactivity but not inattention. Most studies of APAP have shown associations to the former but not the latter. Positive results in a

study of ODD/CD would allow for assessment of coherence with the literature on ADHD in general and APAP use. Thus, it is reasonable to include evidence from the Ruisch study as part of the APAP and ADHD literature.

Like the Stergiakouli report, this study's strength is its adjustment for a biologic measure of genetics taken directly from genome-wide association studies. It was also strengthened by high response rates, specificity of exposure questions, and validation of maternal responses by teacher reports. These features limited selection bias and misclassification. Moreover, like DNBC and MOBA, ALSPAC was a population-wide cohort study, representing substantial generalizability to women in one county in the UK.

Limitations of this analysis were as follows. Reliance on an ever/never categorization for APAP at 32 weeks would have underestimated exposure. Moreover, it would have admixed long and short-duration users. Lack of specificity on timing and duration of use would have biased results toward the null. A further consideration is that outcomes were based on self-report by mothers and teachers and on subjective scales. Evidence of a high correlation between scores by the two respondent groups lends credibility to the results. Nonetheless, in all studies based on psychological scales, there opens the door to inherent bias. In the case of these measures, children can be "labeled" as disruptive and it can be difficult to shed this perception. Again, in that this would not have been related to knowledge of maternal APAP exposure, any misclassification would have been non-differential and biased results toward the null.

Overall, Ruisch et al., in a study of OCC and CD, demonstrated correlations between maternal and teacher reports of behavior. Moreover, they showed a significant 22 to 24% increase in ODD symptom scores after adjusting for genetic confounding. They complement the Stergiakouli results by limiting genetic confounding. The Ruisch results add coherence to those

earlier results in showing another measure of ADHD-related symptoms was significantly associated with maternal APAP use.

Leppert (2019)

Using ALSPAC data as did Stergiakouli and Ruisch (see below under studies reviewed for context). Briefly, ALSPAC was a population-based prospective birth cohort in which 14,150 women residing in Avon, UK were enrolled at 18 weeks gestation and queried regarding exposures during pregnancy at 18 and 32 weeks. In this analysis, the authors correlated many pregnancy-related lifestyle behaviors, toxins, vitamins and supplements, infectious and autoimmune diseases, physical and mental health conditions, and APAP use with genetic risk scores for ADHD. Their hypothesis was that because a confounding factor must relate to both exposure and outcome, demonstration of a link between genetic score to risk factors, including APAP use, suggests the potential for genetic confounding.

Response rates to mailed questionnaires was high (88%) and the APAP exposure question was specific: “Please indicate how often you have taken the following pills in the last three months. (a) Aspirin; (b) Paracetamol; (c) Codeine; (d) Mogadon or other sleeping tablets; (e) Valium or other tranquilizers.”

Outcomes were genetic risk scores among 7,142 pregnant women assessed at 18 weeks and 6,748 pregnant women genotyped at baseline.

Multiple potential confounding variables were included in models as covariates. Since the authors assessed a variety of potential confounders, it is not clear what they adjusted for in their models. Their analyses considered links between ADHD genetic risk scores and smoking,

alcohol intake, four different nutritional supplements, APAP, anti-depressant medications, pre-pregnancy BMI, age at delivery, diabetes, hypertension, preeclampsia, rheumatism, psoriasis, severe depression, infections during pregnancy, vaginal bleeding during pregnancy, stressful life events, blood levels of various toxins, blood vitamin D, blood hemoglobin, Caesarian section, low birthweight, preterm delivery, low APGAR, hypoxia, and breastfeeding at one month. They say their covariates were "ten population stratification principal components derived from unrelated individuals using the Eigenstrat method" plus "perinatal factors." It is not clear what variables comprise these components.

Composite scores of molecular genetic risk factors for ADHD (polygenic risk scores) were calculated for 8,340 ALSPAC mothers using available genotype data using strict quality control protocols and standard internationally accepted methods. Polygenic risk scores were computed using "risk alleles" based on the results of an independent case-control United Kingdom/Ireland ADHD genome-wide association study (GWAS) (discovery sample). In line with previous studies, a threshold of P< .50 was used to select alleles more common in cases than controls from the discovery sample (SNPs in relative linkage equilibrium in the discovery sample GWAS were selected first). These identified SNPs were used to calculate a polygenic score for each individual in ALSPAC, corresponding to the mean number of score alleles (weighted by the logarithm of the odds ratio) across the set of SNPs.

"Ever" use of APAP during pregnancy was associated with an increased risk of ADHD symptoms per analysis in eTable 8 (RR, 1.45; 95% CI, 1.18–1.78). The ADHD genetic risk score was associated with use of APAP during late pregnancy (32 weeks) (OR, 1.11; 95% CI,1.04–1.18). In early pregnancy (18 weeks), risk was also increased (OR 1.09, 95% CI 1.02–1.17), but to a smaller degree.

Leppert Critique.

The authors interpret their data as follows. “We found evidence of an association of smoking (relative risk [RR], 1.70; 95% CI, 1.37–2.10) and use of acetaminophen (RR, 1.45; 95% CI, 1.18–1.78) during pregnancy, ever having depression (RR, 1.64; 95% CI, 1.20–2.25), and an increased stressful life events score (RR, 1.15; 95% CI, 1.10–1.20) with an increased risk of ADHD, as described previously for this cohort.” “Our results suggest that mothers with higher ADHD PRS may also be more likely to use acetaminophen in pregnancy. Whether the association between ADHD and acetaminophen use holds after adjusting for shared genetic factors and represents a causal relationship should be assessed in a causally informative mendelian randomization framework and with other genetically informative designs that test and account for horizontal pleiotropy.” They continue, “Our findings suggest that several early-life factors linked to neurodevelopmental disorders are associated with maternal genetic liabilities to these dis-orders, primarily ADHD. Therefore, to draw conclusions about causality, future studies need to account for potential genetic confounding and triangulate evidence from different causally informative approaches.”

To translate their discussion into less discipline-specific terms, the authors admit that their results simply show that pregnancy-related APAP use is associated with a genetic risk score for ADHD. They did not show directly that genetic risk impacted the association between APAP use and ADHD. To do this, they would have had to compared prenatal use of APAP in mothers of children who developed ADHD vs. those who did not and then control for PRS within such a study. This is not what they did. What they did was to demonstrate that PRS might theoretically have an impact in such a study, not that it did have an impact in such a study. That is what is meant by their discussion point: “Whether the association between ADHD and acetaminophen use holds after adjusting for shared genetic factors and represents a causal relationship should

be assessed in a causally informative mendelian randomization framework and with other genetically informative designs."

The most important point regarding the Leppert study is that PRS scores are very unlikely to reflect true family aggregation. Women who have a diagnosis of ADHD are more likely to have children with ADHD. But this is almost certainly a function of both environment and genetics. The genetic component is what PRS tries but fails to represent. As comprehensively reviewed by Herzig (2022), "The misinterpretation of PRS has dangerous clinical and eugenic consequences." The authors explain, "Unfortunately, it is under erroneous assumptions that these scores are computed. As for heritability estimates, PRS depends on an underlying genetic model that is unknown for most human diseases." And "[t]he Polygenic Additive Liability model, under which PRS is computed, was proposed sixty years ago to explain the familial segregations of a disease that cannot be explained by a monogenic transmission model. Since then, human geneticists have learned that such a model cannot account for the heterogeneity and complexity of pathophysiological processes. The adoption of this model accredits the idea that our diseases are genetically determined and that our genetic risks of contracting a disease are known at birth."

In other words, Herzig and Leppert are both cautioning that the assumptions underlying the use of PRS as a surrogate for genetic risk are flawed. We know so little about the allelic variants that contribute to AHDH that even when combining all of them, they have very little predictiveness. Moreover, the statistical model that underlies PRS analyses is outdated and discounted by geneticists.

Thus, Leppert's study contributes little to resolving the question of genetic confounding.

In other genetically informative designs such as adjusting for family factors and NCE controls, the impact of APAP on ADHD was not eliminated (Stergiakouli 2016, Ruisch 2018).

Leppert used the same data as was used by Stergiakouli and Ruisch (both reviewed below for context only because both were based on behavioral measures of ADHD)—the same APAP exposure data obtained at 18 weeks and 32 weeks and the same genetic risk scores. Stergiakouli evaluated 3,381 maternal/child pairs at 32 weeks whereas Leppert evaluated 6,748 mothers at 32 weeks pregnancy. However, the two participant groups seemed to have similar characteristics in many respects. All of this makes it particularly unclear as to why the theoretical concern raised by Leppert (does APAP use increase genetic risk score) did not translate into actual confounding when employed by Stergiakoui and Ruisch. Again, Stergiakouli and Ruisch both actually applied the genetic risk score to the assessed link between APAP use and ADHD and found no substantial diminution of effect. Said another way, although the Leppert report raises a hypothetical concern about the potential for genetic confounding based on ALSPAC data, that concern did not seem to play out in actual fact.

In summary, Leppert's demonstration of an association between prenatal APAP use and ADHD polygenic risk score raises real concern. However, careful consideration of the use of PRS scores to reflect genetic risk suggests that PRS scores are a poor reflection and poor design that should not be overly relied on. Moreover, the same PRS score that Leppert related to APAP exposure failed to act as a confounder in studies examining the direct association between prenatal APAP use and ADHD behaviors. This detracts from concerns raised.

Inoue (2021)

This study, using data from the Danish National Birth Cohort (DNBC) evaluated the associations of prenatal and postnatal exposures to APAP with behavioral problems in children at age 11 years, using behavioral measures reported by parents and children.

Design characteristics were described above (see Liew 2014). This analysis is an update to that earlier study, which also assessed ADHD-related childhood behaviors on the SDQ, but at age 7. The authors included 40,934 mother-child pairs from the DNBC enrolled during 1996 to 2002.

In addition to maternal reports of prenatal use of APAP, the authors also explored their reports of using the medication for their child (postnatal use) in relation to outcomes. Information regarding acetaminophen exposure during infancy was ascertained through computer-assisted telephone interviews at about 6 and 18 months postpartum. Mothers were asked to report whether their children had experienced any of 16 types of conditions or diseases and the specific pharmaceutical treatment for these conditions.

Parent-reported and child-reported SDQ responses were collected during the 11-year follow-up interview. RRs were calculated for behavioral problems including total difficulties as well as internalizing or externalizing behaviors.

Parent-reported and child-reported SDQ scores were moderately correlated; higher for externalizing (r=0.59) than internalizing (r=0.49) behaviors. After adjustment for relevant confounding factors, prenatal APAP exposure was associated with 10 to 40% higher risks for SDQ total difficulties and internalizing and externalizing problems based on parent- or child-reported SDQ, with risks somewhat higher based on child reports. For total difficulties, parent-reported RR was 1.14, 95% CI 1.01–1.29, child-reported RR was 1.40, 95% C: 1.20–1.63);

internalizing problems, parent-reported RR was 1.09, 95%CI 1.00–1.19, child-reported RR was 1.13, 95% CI 1.04–1.23; and externalizing problems, parent-reported RR was 1.07, 95% CI 0.99–1.15, child-reported RR was 1.13, 95% CI 1.05–1.22.

APAP use for >10 weeks was associated with an elevated risk for a child having an SDQ total difficulty score of ≥17 (RR of 1.32, 95% CI 1.06–1.63, p trend=0.03) based on parent report and also based on child report (RR 1.58, 95% CI 1.22–2.06, p trend <0.01). Children also reported significantly increased risk of internalizing behaviors after >10 weeks of exposure (RR 1.27, CI 1.08–1.48 p trend <0.01).

For duration of APAP exposure, RRs were as follows: 1.07 (95% CI 0.92–1.23) for 1-5 weeks, 1.27 (0.95–1.70) for 6-10 weeks, 1.32 (1.06–1.63) for >10 weeks. For the estimates of 1-5 weeks and 6-10 weeks, the two CIs were entirely overlapping so these estimates are not statistically different from each other. The appropriate interpretation of these data, then is that, despite the differential in statistical significance, women with a duration of APAP use of 6+ weeks (42 days) were at increased risk.

Postnatal exposure was associated with parent-reported total difficulties (SDQ ≥17 RR = 1.18, 95% CI: 0.95–1.48) and parent-reported internalizing behaviors, (RR = 1.15, 95% CI: 0.98–1.35), but the 95% confidence intervals of these effect estimates included the null. No elevations in risk were seen for child-reported scores on any of the SDQ metrics related to post-natal use.

Inoue Critique

Little more can be said about this analysis than was said about the Liew analysis. Both had the same strengths and suffered from the same weaknesses.

One additional strength of the study was rating of SDQ behaviors by the child as well as the parent, which provided more depth to the result and added an internal validation.

Another strength of this study was that it reported the effects of postnatal exposure to APAP, all of which were marginal and none of which reached statistical significance. As discussed above in the Liew (2019) analysis of NHS II, post-natal APAP use can be considered a kind of negative control (NCE) in that it was not expected to causally affect the outcome but shared a similar confounding structure with the exposure variable of interest. Indeed, in this analysis, postnatal exposure did not substantially impact ADHD-like behaviors on the SDQ.

Overall, Inoue updated the former Liew analysis and carried the result into early adolescence. The study showed that at age 11, children and parents both reported ADHD-like behavioral difficulties overall, as well as in internalizing and externalizing behaviors, consistent with much previous research. They also showed a duration-response relationship. Post-natal APAP exposure was not significantly related to ADHD.

Alemany (2021)

A pooled analysis based on six European cohort studies was designed to address the relationship between APAP use during pregnancy and ADHD. A total of 73,881 mother–child pairs were included in the study.

Cohorts included were: Avon Longitudinal Study of Parents and Children (ALSPAC) from UK, DNBC from Denmark, Gene and Environment: Prospective Study on Infancy in Italy (GASPII), the Generation R Study from the Netherlands, Infancia y Medio Ambiente (Environment and Childhood) (INMA) from Spain, and the Mother–Child Cohort in Crete (RHEA). All recruited

mother–child pairs from 1991 through 2008. The design of ALSPAC and DNBC have been reviewed in detail above.

Prenatal and postnatal (up to 18 months) APAP exposure were assessed through maternal questionnaires or interviews. Mothers were interviewed two (INMA, RHEA), three (GASPII) or four (DNBC) times during pregnancy using standardized questionnaires. At each interview, mothers were asked if they had taken medications from the month before becoming pregnant (GASPII; INMA) or beginning of pregnancy (RHEA), through delivery. In ALSPAC and the Generation R Study, mothers completed questionnaires two (ALSPAC) or three (the Generation R Study) times during pregnancy reporting acetaminophen use from the month before becoming pregnant to gestational week 32 of pregnancy. In GASPII, mothers were interviewed at birth and provided retrospective information on acetaminophen use at each trimester.

In order to harmonize this large variability in exposure assessments, Alemany classified APAP use during pregnancy as ever exposed if they reported having taken any dose of APAP in the defined prenatal exposure period; otherwise they were classified as non-exposed.

ADHD symptoms were assessed at 4–12 years of age using a variety of validated instruments. (ADHD symptoms were assessed using the DAWBA (ALSPAC); the Conner's Parent Rating Scale (CPRS-R:S) (The Generation R Study), the SDQ (DNBC), the Attention Deficit and Hyperactivity problems subscale of the CBCL (GASPII and RHEA), and the DSM-ADHD Questionnaire (INMA) (acronyms only are used for scales previously discussed). In all of these instruments, higher scores indicate more symptoms. DNBC, in addition to the SDQ-Hyperactivity/Inattention sub-scale used diagnoses of ADHD from their national hospital register.

To harmonize the continuous scores on ADHD symptoms, the authors used questionnaire-specific validated cut-offs to yield categorical proxies for ADHD symptoms and validated lower cut-offs for borderline symptoms.

Analyses were adjusted for child and maternal characteristics along with indications for acetaminophen use. Adjusted cohort-specific effect estimates were combined using random-effects meta-analysis. Potential confounding variables were selected a priori and prioritized availability and consistency. Covariates were factors previously associated with ADHD and APAP exposure and include maternal and child characteristics. Maternal characteristics included age at delivery (years), education (low, medium, high), pre-pregnancy BMI, alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, >1 and >2), maternal fever (yes/no) and infections (yes/no) during pregnancy. Child characteristics included sex, age at behavioral assessment (years), cold (yes/no) and respiratory infections (yes/no) in the first 2 years of life. Maternal characteristics were collected during pregnancy except for mental health in INMA, which was collected when children were around 5 years. Child characteristics were collected in the first 18 months of life.

APAP use during the prenatal period was reported by 14 to 56% of mothers, with RHEA having the lowest proportion and DNBC the highest. A wider range of child postnatal APAP exposure was reported varying from 6% in ALSPAC to 92.8% in GASPII. The proportion of children having borderline/clinical symptoms ranged between 1.2 and 12.2% for ADHD.

The odds of developing ADHD symptoms within the borderline/clinical range were 21% higher among children prenatally exposed to APAP compared to non-exposed children (OR=1.21, 95% CI 1.07–1.36). Prenatal APAP use was associated with ADHD symptoms in boys (OR=1.23,

95% CI 1.05–1.44) and to a similar extent in girls (OR=1.18, 95% CI 0.97–1.44). Results were similar in leave-out analyses and in DNBC registry data. Additional adjustment for confounders did not change the results. There was no evidence of study heterogeneity.

In the Discussion section, the authors' interpretation of their results was as follows. "The most consistent pattern of results was observed for the association between prenatal acetaminophen exposure and ADHD symptoms. The positive associations were observed in all the cohorts and of similar magnitude regardless of the cohort excluded in the leave-one-out analysis. This finding is in agreement with previous meta-analysis which reported likelihood increases of 25% and 34% for ADHD in relation to prenatal acetaminophen exposure. Our findings are consistent with previous single cohort studies conducted in ALSPAC, DNBC, and INMA cohorts, which were included in our meta-analysis. Despite the overlap of samples included, this agreement supports the robustness of the findings since analytical strategies and outcome definitions were harmonized for the present meta-analysis."

Alemany Critique.

In my estimation, this study is uniquely strong in many respects. It is based on a large and heterogeneous sample. Validated instruments for behavioral assessment were used as were established cut-offs. Adjustment was made for many relevant confounders. Data were pooled rather than combined via meta-analysis. That is, original data were used rather than relying on reported effects. Both clinical and borderline diagnoses were assessed. Postnatal exposure was analyzed. Uses of a harmonized definition of exposure and outcome as well as of common statistical approaches were also strengths. The homogeneity of the findings among the different cohorts each with a different prevalence of APAP use and neurobehavioral diagnoses greatly enhanced the validity of the overall finding.

Nonetheless, as with all studies, there were limitations. First, ADHD symptoms were assessed by different instruments in the cohorts. This was overcome by using instrument specific cut-offs. Although cohorts differed in the prevalence of ASC and ADHD symptoms, associations were largely consistent.

Second, confounding by indication cannot be completely ruled out although potential indications for APAP use were included as covariates (i.e., maternal fever or infections during pregnancy, maternal chronic illnesses, and child cold or infections in the first 18 months of life).

Third, dose and frequency of use were not harmonized across cohorts and therefore, only an ever/never use variable was considered. This surely represents an underestimate of the true effect size.

Fourth, given the high rates of loss to follow-up in some of the included cohorts, selection bias could have impacted the results. However, loss to follow-up was low (<2%) in the largest cohort (DNBC) when based on hospital diagnoses, and DNBC registry data produced consistent findings compared to all the other cohorts together. If anything, DNBC data yielded somewhat larger effect sizes.

In summary, the authors conclude as follows, “our results support previous findings and address part of the weaknesses of previous meta-analyses. Considering all evidence on acetaminophen use and neurodevelopment, we agree with previous recommendations indicating that while acetaminophen should not be suppressed in pregnant women or children, it should be used only when necessary.”

I regard Alemany as one of the strongest studies in the literature for its size and scope. It showed effects on the order of magnitude of 21% increased risk for behavioral measures of ADHD. Because it was based on an ever/never use exposure categorization, these are almost surely underestimates. The consistency of results across studies is notable.

BRADFORD HILL ANALYSIS

I now turn to a discussion of the criteria set out by Bradford Hill in his 1965 address, one of the universally accepted standards for assessing causation. As Bradford Hill makes clear, none of the factors are required other than temporality, i.e., there cannot be causation if the effect occurs before the supposed cause. However, as he states, “None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non.” (Hill 1965)

Strength of association

Reasonable epidemiologists and clinicians today consider statistical significance as well as the magnitude of observed risks when evaluating strength of association. (Fedak 2015) However, the classic Bradford Hill approach considers only the magnitude of the RRs and holds that statistical significance is not the equivalent of clinical/public health import. The later stance is accepted by the most eminent statisticians in the profession as well as the American Statistical Association. It is also the stance accepted by the most prominent epidemiologists in the field (see above regarding statistical significance for a more complete discussion and references). I adhere to and employ the classic Bradford Hill approach of focusing on risk magnitude, but I also discuss the precision with which that magnitude has been shown.

The strength of the association between APAP use and ADHD can be summarized as follows. I have identified 9 studies: 7 observational cohort studies (Liew 2014, Ystrom 2017, Ji 2018, Liew

2019, Ji 2020, Baker 2020, Gustavson 2021), 1 nested case-control study (Chen 2019), and 1 metanalysis (Ricci 2023) that examined ADHD use during pregnancy and diagnosed ADHD. These have been reviewed in detail above. Additional studies and meta-analyses examining behavioral measures correlated with ADHD diagnosis were also reviewed for context—but were not included in my strength assessment. (Brandlistuen 2013, Stergiakouli 2016, Liew 2016, Avella-Garcia 2016, Ruisch 2018, Leppert 2019, Masarwa 2020, Inoue 2021, Alemany 2021.) Of the 9 studies and meta-analysis that contribute to my Bradford Hill assessment, the populations are from the U.S., Canada, and Europe. Most are of large or very large magnitude. For instance, the 4 studies pooled in the Ricci meta-analysis constituted 122,294 mother/child pairs. Exposure measures included maternal recall, cord blood, maternal blood, and meconium. All 9 studies demonstrated statistically significant, positive associations between APAP use during pregnancy and diagnosed ADHD. Not all showed statistically significant effects in all sub-analyses—including the Gustavson sibling control analysis, which I discuss in detail below—but as noted repeatedly, statistical significance is not the method by which I evaluate strength.

Although some of the RRs in the studies using biomarkers for exposure were strong—with RRs well above 2.0—most RRs in this literature shows associations that are modest in magnitude (typically ranging between 1.2 and 1.6). This degree of risk was best characterized by Ricci in their meta-analysis, as “small to moderate.”

Although the associations reported for prenatal APAP and ADHD are modest, that in no way suggests they are not causal. As even Bradford Hill pointed out, there are many real causal associations that are not particularly strong. As he put it, “we must not be too ready to dismiss a cause-and-effect hypothesis merely on the ground that the observed association appears to be slight. There are many occasions in medicine when this is in truth so.” “Examples include the

associations between air pollution and mortality, between smoking and heart disease, and between environmental tobacco smoke and lung cancer." (Rothman 2008, p 19).

Examples of other associations in the range of 1.3 to 1.4 that are considered causal are discussed in detail above (see pp. 5-7) and repeated here. Notably, in each of these situations, the more modest association was not only accepted as causal by the epidemiologic community, but it changed clinical opinion and public health practice.

Example 1: Occupational exposure to Benzene and risk of leukemia: In 2010, a meta-analysis of 15 epidemiologic studies found that worksite benzene exposure increased risk of any leukemia by 40% (relative risk 1.40, 95% CI 1.23–1.57). (Khalade 2010) On the basis of this literature and support, benzene is considered a cause of leukemia and is regulated as such.

Example 2: Estrogen-progestin menopausal hormone therapy (HT) and breast cancer risk: The Women's Health Initiative clinical trial showed that this type of HT increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke). (Rossouw 2002) A meta-analysis of clinical trials and observational studies in 2018 found that use of this therapy increased risk of breast cancer by 59% (relative risk 1.59, 95% CI 1.40–1.81). (Kim 2018) These results led to FDA-required label warnings on estrogen and progesterone therapy preparations, and to clinical warnings against use of estrogen plus progesterone for prevention of chronic conditions. (Grossman 2017)

Example 3: Trichloroethylene and risk of kidney cancer: In 2012, a meta-analysis was published showing that occupational exposure to trichloroethylene was associated with an approximately 30% increased risk for kidney cancer (relative risk 1.32, 95% CI 1.17–1.50). (Karami 2012) This and other evidence resulted in Trichloroethylene being reconsidered by IARC, which then deemed it Group 1: carcinogenic in humans.

Example 4: Talc and ovarian cancer: The elevated risk from talc use is an 8 to 30% excess risk as indicated by several meta-analyses. For example, a pooled hazard ratio (HR) from cohort studies was 1.08 (0.99–1.17), on the edge of significance. The HR for women with a patent tract was 1.13 (1.01–1.26). (O'Brien 2020) Also, Taher (2018) included 27 studies, three of which were cohorts and reported an overall estimate for perineal use of talc of 1.28 (1.20–1.37) in relationship to ovarian cancer. There was no evidence of heterogeneity and study quality did not substantially impact the estimates. Similarly, Penninkilampi (2018), who studied 24 case-control studies and 3 cohorts. The overall estimate for perineal talc use in association with ovarian cancer was 1.31 (1.24–1.39) with no evidence of heterogeneity.

Example 5: Air pollution: Exposures that are common, even though their association is modest or even "weak" can cause large numbers of cases. The World Health Organization (WHO) estimates that as many as 99% of the world population breathes air that exceeds WHO air quality limits. Because a large proportion of the population is exposed to the risk factor, even a small increase in risk can result in a large number of people suffering from fatal diseases or conditions in excess to those who would have suffered in the absence of the exposure. The Lancet commission on air pollution and health estimated that air pollution caused 9 million deaths globally in 2019. (Landrigan 2018) Yet, air pollution has a weak association with the risk of death. The most definitive meta-analysis of air pollution and death reported a relative risk of 1.06 (RR = 1.06, 95% CI = 1.05–1.07) for an increase of 100 μg/m3 increase in total particle

concentrations in ambient air. (Schwartz 1994) A relative risk of 1.06 indicates that there is only a 6% increase in the risk of death associated with the exposure. Most people globally are exposed to air pollution, thus, this small excess risk associated with air pollution results in tremendously high numbers of deaths globally. In sum, exposures that are common can have a significant impact on public health, even if the relative risk associated with the exposure is small. It is important to consider both the relative risk and the prevalence of an exposure when assessing its impact on the population. (Though as stated above, the relative risk is principally what matters when evaluating the strength factor of Bradford Hill.)

Returning to the question of APAP and ADHD, when examining the APAP data more carefully by number of trimesters used, RRs for use in all three trimesters were 1.27–1.61 (Liew 2014; Ystrom 2017). Long duration use RRs ranged from 1.78-2.20 (Liew 2014, Ystrom, Ricci).

The most sensitive period for APAP use in relation to ADHD appeared to be later in pregnancy, particularly in the third trimester. Use in the first trimester produced RRs of 1.09–1.31 and in the second trimester, 1.13–1.20. (Ystrom 2017, Chen 2019). In contrast, APAP use during the third trimester (Liew 2014, Ji 2018, Gustavson 2019, Baker 2020, Ji 2020) ranged from 1.28–2.86. In the third trimester, use of APAP was associated with ORs of 1.88–2.86 in four of five studies.

Only one meta-analysis reported a summary OR for ADHD using diagnostic endpoints. (Ricci 2023). Masarwa estimated the odds of developing ADHD based on diagnostic and behavioral outcomes. As noted above, it is included as one of the studies that informed the Hill analysis only because the Court referenced it extensively in its decision. Its inclusion does not change the analysis—indeed, it bolsters it. The Masarwa OR was 35% (OR 1.35, 95% CI 1.25–1.46). After selection bias correction the result was a corrected RR of 1.31 (95% CI 0.91–1.71). When correcting for exposure misclassification, the risk estimate increased even further to 1.91 (95%

CI 0.04–3.77) but the confidence intervals became markedly unstable. Such a degree of uncertainty made this estimate difficult to interpret for evaluating strength.

Ricci performed a meta-analysis of four studies (Baker 2020, Ji 2020, Liew 2019, Ystrom 2017) that each used ADHD diagnosis as an endpoint. Each of the individual studies reported a significant positive relationship between prenatal APAP use and ADHD, ranging from 1.12 to 2.25. The meta-analytic pooled risk estimate, adjusting for maternal and infant characteristics was 1.47 (95% CI 1.12–1.92). The fully adjusted pooled RR was strongest for the longest duration of exposure (pooled RR 1.84 95% CI 1.46–2.31) wherein there was limited heterogeneity. Age at assessment had little affected the pooled RR. Finally, when the authors excluded women with fever, the pooled RR remained elevated (pooled RR 1.61 95% CI 1.21–2.13), again with low study heterogeneity.

Likely the most impressive study in the literature to date has been that conducted by Baker in Quebec in which exposure was determined based on a biologic measure of cumulative exposure over the final two trimesters of pregnancy (meconium) and ADHD was diagnosed by a health professional among 345 children aged 6 to 7 years. APAP was detected in 199 meconium samples (58%) and ADHD was diagnosed in 33 children (10%). After probability weighting with propensity scores to account for potential confounders, including child sex, familial income, maternal age, education, pre-pregnancy BMI, smoking during pregnancy, alcohol during pregnancy, and maternal self-reported ADHD, APAP detected in meconium was associated with an OR of 2.44 (95% CI 1.41–4.22). This represents one of the stronger links in the literature. The strength of the study design lends credence to the supposition that other studies, reliant on maternal report of exposure and outcomes, were likely biased toward the null.

The other studies that used a biomarker of APAP exposure and the outcome of ADHD were Ji (2018) and Ji (2020). Based on maternal serum measurements of APAP concentration in 996 women from Boston followed until their children were 7, Ji (2018) ascertained ADHD outcomes from diagnoses in the hospital electronic medical record database. Children with the highest level of exposure (top tertile) were 58 to 88% more likely to develop ADHD than those without APAP in maternal blood. Using the same cohort and outcomes but now using cord blood as the metric for APAP exposure (2020), Ji found that being in the second and third tertiles of cord APAP burden, as compared to the first study, which was associated with odds of an ADHD diagnosis of 2.26 (95% CI 1.40–3.69; second tertile) and OR of 2.86 (95% CI 1.77–4.67; third tertile).

Thus, the studies using biologic measures reported higher risk values than studies based on self-report or medical records. The import of reliance for causal assessment on studies using better measures and methods has been emphasized in applying Hill's criteria as per Thomas Frieden, Director of the CDC. "Studies that use better measures and methods are more likely to show actual health effects." (Cogswell 2016)

Overall, the association between recalled ever/never prenatal APAP use and ADHD diagnosis was modest. For long duration users, it was more pronounced and, in fact (RR 1.78–2.20) close to 2.0. Moreover, risk estimates from studies using biologic biomarkers of exposure also showed larger effect sizes (RRs 2.44–2.86). Nonetheless, to be conservative, I consider the effect size to be modest.

To be sure, when an association is weaker, it becomes more important to examine potential sources of confounding. "A strong association can help to rule our hypotheses that the association is entirely due to confounding or other bias" (Rothman 2008). But the study authors

and I have examined that possibility in great detail (see below) and neither they nor I believe it entirely accounts for these risk estimates. Indeed, bias, particularly misclassification bias secondary to poor maternal recall, and use of a crude (ever/never use) metric may have resulted in reducing observed risks as compared to actual risks.

I placed moderate weight on the tenet of strength of association because, although a strong association is particularly likely to be causal (e.g., the double-digit risk ratios observed for tobacco and lung cancer), there are many instances when associations are weak or moderate even though they are causal.

Based on the above considerations, I consider the criterion of strength of association to be only partially met.

Consistency

Overall, the results of studies linking *in utero* APAP exposure to diagnosed ADHD are almost uniformly positive, and mostly statistically significant. The few non-statistically significant results do not mean the literature is inconsistent. As the long-standing editor of the journal *Epidemiology* and author of the leading textbooks, *Introduction to Epidemiology* and *Modern Epidemiology*, Kenneth J. Rothman cautions, it is “completely fallacious” to say that “a literature or set of results is inconsistent simply because some results are ‘statistically significant’ and some are not.” (Rothman 2008)

For a concrete example of why, consider an analysis of water contamination and illnesses. The Agency for Toxic Substances and Disease Registry (ASTDR), a federal public health agency of the U.S. Department of Health and Human Services, assessed in detail the evidence in support of a causal link between exposure to contaminated water at Camp LeJeune and the

development of numerous illnesses. When evaluating that evidence, ASTDR noted—citing Rothman—that "in our assessment, we did not use confidence intervals to determine whether a finding was 'statistically significant' nor did we use significance testing to assess the evidence for causality." (ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases (January 13, 2017)) Their reasoning, with which I agree, was that "a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association."

In its assessment of the literature on APAP and ADHD, the FDA has written, "in general, the functional neurobehavioral outcome studies examined in this review along with the reviewed meta-analyses suggest a consistent association between APAP or long durations of prenatal APAP exposure and ADHD." (FDA CDER Epidemiology: Review of Published Studies (July 15, 2022), FDACDER000114)

Consistency does not mean perfect consistency. Some outliers are to be expected in any literature—even the secondhand smoke literature has some null (and even negative) results. (Surgeon General, The Health Consequences of Involuntary Exposure to Tobacco Smoke, 2006)

Meta-analyses by Ricci and Masarwa showed remarkable consistency (see Forest Plot in Masarwa and Figure 3 in Ricci).

With only a small handful of exceptions, meta-analyses, pooled analyses, and individual cohort studies conducted over the past 15 years have consistently found an association between APAP use during pregnancy and ADHD. Although at first, the range of estimates appears broad, when broken down by duration of use, the range turns out to be far narrower. In the

meta-analyses, the range for ever/never use was 1.31–1.91 (Masarwa 2018 and 2020, Ricci 2023). By number of trimesters used, for all trimesters RRs were 1.27–1.61. (Liew 2014, Ystrom 2017) Long duration use RRs ranged from 1.78–2.20 (Liew 2014, Ystrom 2017, Ricci 2023). Moreover, using biomarkers of exposure, risks for ADHD were elevated by 214 to 362%.

APAP and ADHD association studies were conducted in an array of large prospective studies, representing the most comprehensive and carefully conducted pregnancy and birth cohorts in the world. Cohorts are considered the most valid designs among observational studies, reflecting less selection and misclassification bias than case-control or cross-sectional designs. These cohorts came from multiple countries, were conducted over multiple time periods, and used numerous measures of exposure and outcome. The great majority demonstrated dose-response relationships (see below), identified a specific window of sensitivity (second and/or third trimester), and excluded other potential APAP-associated outcomes. Many attempted to demonstrate that bias or confounding may have accounted for the association between APAP use and ADHD and showed that, although confounding may have *partially* contributed to the observed risk, it did not likely explain all of it. And bias acted in the opposite direction, making the observed risk likely to be understated. (Masarwa 2020)

Study strengths complimented each other. Some studies excluded confounding by indication; others limited confounding by genetics; others used biologic exposure measures; others registry, psychiatric diagnosis or MRI outcome measures, curbing misclassification. In aggregate the consistency of positive results when applying these various strategies strongly argues against systematic bias. The consistency observed in the APAP and ADHD association studies aligns with the concept of triangulation in epidemiology. As defined by Lawlor et al., triangulation is “[t]he practice of strengthening causal inferences by integrating

results from several different approaches, where each approach has different (and assumed to be largely unrelated) key sources of potential bias." (Lawlor 2016) This concept emphasizes strengthening causal inference by integrating results from varied approaches, each with unique biases. The consistent findings across different cohorts, methodologies, and timeframes in the APAP studies, despite their varied potential biases, effectively exemplify the application of triangulation, bolstering the validity of the findings.

As a counterexample to the degree of consistency seen in the APAP literature, consider the epidemiologic argument for valproic acid and ADHD. Valproic acid has been established to cause ADHD when taken in pregnancy. As the Court noted in its order, the DSM describes valproic acid as a risk factor for neurodevelopmental disorders (Order at 13), and the valproic acid label specifically states that valproic acid likely causes ADHD.

One large cohort study from Denmark linked prenatal valproic acid use, but not other anti-epileptic medications, to ADHD risk (reviewed in more detail below under Analogy). Children with prenatal valproate exposure had a 48% increased risk of ADHD (adjusted HR 1.48; 95% CI, 1.09–2.00) compared with children with no valproate exposure. (Christensen 2019) In a meta-analysis, only 2 other cohort studies met the inclusion criteria. Both showed positive associations in the range of 1.51–2.84 but neither found statistical significance. (Veroniki 2017). Notably, then, valproic acid was accepted as an established risk factor based on only three cohort studies, only one of which was statistically significant. In contrast, the literature on prenatal APAP and ADHD includes 11 studies with diagnostic endpoints and 8 additional studies with behavioral endpoints.

Consistency is a particularly compelling component of Hill's criteria. This is the reason that meta-analyses focus on the degree of heterogeneity among studies. The more heterogeneous

the ORs (or HRs), the greater the concern about combining study results. Two meta-analyses and pooled analyses of prenatal APAP use and ADHD have shown no significant heterogeneity (Masarwa 2018, Ricci 2023).

I placed great weight on the tenet of consistency. Quoting from the long-standing editor of the journal *Epidemiology* and author of the leading textbook in epidemiologic methods, "the presence of a consistent result is often taken as a compelling argument for causality." (Rothman 2008). The question for consistency is (in Bradford Hill's formulation) whether the association has been "repeatedly observed by different persons, in different places, circumstances, and times." (Hill 1965) Given the above analysis, I conclude in the affirmative.

I place heavy weight on the criterion of consistency as did Rothman (2008) and Hill (1965). Based on the above considerations, I believe that the criterion of consistency is met.

Biologic Plausibility

The criterion of Biologic Plausibility is just what its name suggests. It is not about the identification of a definitive biologic pathway but instead a plausible explanation for the biology underlying a cause-effect relationship. In the words of Rothman, "A causal explanation is plausible if it appears reasonable or realistic within the context in which the hypothesized cause and its effect occur. This context includes not only epidemiologic but also other human studies, animal and tissue studies, and current under-standing of the biology, pathology, toxicology, and other mechanisms related to the effect." (Rothman 2008)

Bradford Hill (1965) made clear that biologic plausibility is neither necessary nor sufficient for causation—it merely bolsters the case for causation that is evident from the human

epidemiology. He said, biologic plausibility "is a feature I am convinced we cannot demand" because "what is biologically plausible depends upon the biological knowledge of the day." As the Rothman textbook (*Modern Epidemiology*) notes, the criterion is satisfied so long as the mechanism "appears reasonable or realistic." The Court noted that "scientists have at best developed hypotheses" about the mechanism by which APAP can lead to ADHD. (Order at 92). I agree with the Court in the sense that a hypothesis is something that a scientist believes is true (based on the current evidence) until it is falsified by additional evidence. That is all that is required for this factor to be satisfied—a reasonable hypothesis about how causation would be plausible given what we know about the underlying biology.

There are enumerable examples of exposures we currently consider causal, yet we do not fully understand and for which we can only posit the underlying biologic mechanism. APAP itself works by an unestablished mechanism in providing analgesia. And yet everyone still rightly believes that APAP *causes* pain relief. Going back to the examples cited in the section on Strength of Association, none of the mechanisms driving the biology in the relationships between hormone therapy and breast cancer, and air pollution and death, have been elucidated with 100% certainty. Even smoking and lung cancer remains a causal link with only reasonable biologic explanations, none of which has been established as definitive, that is, a pathway wherein intervention could reduce or prevent disease.

Thus, I considered the case for biologic plausibility based on data from animal studies, and *in vitro* studies that provide reasonable, but not established, explanations.

The human brain is a markedly complex organ, and its development in utero is correspondingly complex. The neural tube forms within the first three weeks of gestation. From there, the cells which will comprise the brain begin a rapid period of proliferation, migration and differentiation

during the first trimester of pregnancy. Synapses form connections between neurons, becoming the basis for cognition While the brain continues to develop throughout infancy and childhood, the great majority of brain development occurs in utero. In order for normal brain development to occur, a huge number of molecular and cellular processes must take place unperturbed. Disturbing these processes can lead to lifelong issues, including ADHD.

One of the ways that altering the levels of oxidative stress has the potential to disrupt neural development is through the fundamental role of oxidative stress in both cellular proliferation and cellular differentiation. The balance of oxidative stress ("redox") and glutathione acts as a signaling mechanism for developing cells. By altering the level of glutathione and redox, "redox signaling pathways can be activated or deactivated," in particular the signaling pathways that govern both cellular proliferation and differentiation. (Hansen & Harris 2015, Dennery 2007).

Studies have demonstrated that "the progression and cessation of proliferation is reliant upon intracellular redox status" i.e. the level of oxidative stress. (Hansen & Harris 2015). When levels of oxidative stress are relatively low, "cellular proliferation machinery is highly active." (Hansen & Harris 2015). As glutathione declines and the cellular environment becomes more oxidized, then "proliferation 'slows' and cells begin to differentiate." (Hansen & Harris 2015, Dennery 2007).

Because NAPQI is highly reactive oxidant molecule that can be neutralized by glutathione, the presence of NAPQI in the developing brain affects the levels of glutathione and redox. If NAPQI reaches a region of the developing brain when the redox balance is at the tipping point between proliferation and differentiation, then even a relatively small amount of NAPQI (by itself or in combination with other factors that affect oxidative stress) will perturb proliferation and differentiation of brain cells.

During differentiation, neural stem cells differentiate into neuronal progenitors, which differentiate into different types of neurons, including dopaminergic neurons, noradrenergic neurons, glutamatergic neurons, serotonergic neurons, and GABAergic neurons. Perturbing the rate and timing of neuronal proliferation and differentiation in the developing brain may therefore perturb the quantity and type of neurons in different regions of the brain, including neurons responsible for the neurotransmitters dopamine, noradrenalin, GABA, and glutamate. There is substantial evidence that the attention deficits and hyperactivity symptoms of ADHD are the product of altered brain structures and dysfunction of key neurotransmitter circuits involved in attention, executive function, reward, excitability, and inhibition, including the neurotransmitters dopamine, noradrenalin, serotonin, GABA, and glutamate. (Buitelarr 2019, Khoury 2022, Farone 2015).

A unique study that lends credence to a direct biologic effect between APAP exposure and adverse neurodevelopment was conducted by Baker (2020). Children with APAP detected in meconium were evaluated using functional MRI brain imaging. The study showed increased negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices among children with psychiatrist-diagnosed ADHD. Children with decreased connectivity were more hyperactive (p= .03) by maternal report. Causal mediation analysis revealed no total or direct effect of meconium APAP levels on hyperactivity, but a significant indirect effect on increased hyperactivity mediated through frontoparietal network and right precentral/frontal gyrus connectivity (14%; 95% CI, 1%–26%). This is exactly the network implicated in the etiology of ADHD. It strongly suggests an anatomic pathophysiology results from prenatal APAP use, a credible biologic pathway directly linking exposure to symptoms of ADHD.

Several authors have addressed the question of biologic plausibility and stated that they believe there are plausible biologic pathways by which the APAP-ADHD link occurs. To my knowledge, there have not been any authors who discounted the presence of realistic pathway(s) underlying this relationship. To quote from Alemany (2021) in the Discussion section from their meta-analysis, “the mechanisms proposed to underlie the adverse effects of early acetaminophen exposure on neurodevelopment include the stimulation of the endocannabinoid system, changes in brain-derived neurotrophic factor (BDNF) levels, oxidative stress due to inflammation-induced immune activation, changes in neurotransmission and endocrine-disruptive properties of acetaminophen. Acetaminophen exposure during periods equivalent to third trimester of pregnancy in humans but not later, induced behavioural and cognitive alterations in both male and female mice. Other animal studies report findings that may be particularly interesting for ADHD. For instance, maternal exposure to acetaminophen was associated with lower levels of BDNF at the level of the striatum in an animal study conducted in male rats. Furthermore, in male mice, acetaminophen treatment induced alterations in spatial learning, memory and dopamine metabolism. Both the striatum region and dopamine are thought to play a pivotal role in ADHD. The abovementioned findings provide biological plausibility and coherence for the current findings.”

Similarly, Chen (2019) states, “Several biologically plausible contentions regarding the effect of prenatal acetaminophen exposure on the risk of neurodevelopmental impairments, including ADHD, have been reported. First, acetaminophen may alter the intrauterine immune system and increase the predisposition for oxidative stress and inflammation, which disrupts the normal development of microglia and their interaction with neurons.”

Animal studies

The oxidative stress hypothesis has further support in animal studies that have demonstrated that exposure to APAP during brain development can result in offspring with altered levels of the neurotransmitters dopamine, noradrenalin, serotonin, glutamate, and GABA:

- "early paracetamol exposure produces major change in serotonergic and dopaminergic neurotransmission in the prefrontal cortex and striatum" (Blecharz-Klin 2017)
- "increased the level of GABA" in the prefrontal cortex (Blecharz-Klin 2014)
- "increases glutamic acids in the spinal cord" (Blecharz-Klin 2015)
- altered "serotoninergic, noradrenergic and dopaminergic system" (Blecharz-Klin 2015a)
- "paracetamol had a significant effect on dopaminergic and noradrenergic neurotransmission" (Blecharz-Klin 2019) and
- "intensified response of male pups to the dopaminergic agonist apomorphine" (Rigobello 2021)

Not every animal study, however, has found the same effects on neurotransmistters. For example, for certain neurotransmitters, Blecharz-Klin (2014) did not find the changes that were later detected in Blecharz-Klin (2017).

Pre- and perinatal APAP exposure, even at low therapeutic doses, has been shown to increase the risk of brain and behavioral abnormalities in rodents. Examples are as follows. Klein et al (2020) force fed Wistar rats with APAP (350 mg/kg/day) or water from gestational day 6 until delivery. Gestational exposure to APAP impaired nest seeking behavior, augmented apomorphine-induced behavioral stereotypy and decreased rostral grooming. Blecharz-Klin (2017) demonstrated major changes in serotonergic and dopaminergic neurotransmission in the prefrontal cortex and striatum. They also found substantial effects on spatial memory and exploratory behavior such as lower motor activity and crossings of a maze during a probe trial.

In another study by the same group (Blecharz-Klin 2018), daily maternal administration of 5 mg/kg or 15 mg/kg of paracetamol to pregnant rats led to almost two-fold decreases in brain-derived neurotrophic factor (BDNF) in prefrontal cortex, hippocampus and striatum. Exposed animals exhibited a lower total frequency of social interactions and social sniffing compared to exposed rats exposed to paracetamol.

Rodent studies have been consistent with the epidemiological data in suggesting that the strongest effects of long-term exposure occurred at a time equivalent to the beginning of the third trimester of pregnancy, a finding coherent with the demonstration that CYP2E1, the enzyme that catalyzes the production of pro-inflammatory NAPQI and leads to oxidative stress/inflammation, is not detected in fetal brains until 17 weeks of pregnancy. (Dean 2012; Philippot 2017) From this, it is logical that APAP toxicity, at least via this pathway, emerges during the second trimester.

Several pathways have been posited to explain the link between APAP use and ADHD. The three with the most clinical and experimental evidence are the alternations in the cannabinoid system; endocrine disruption; and triggering of inflammation/oxidative stress. Below I will discuss this last possibility, as I consider it the most compelling.

Acetaminophen mechanism of analgesic action

Despite its ubiquity as an analgesic, the mechanism of action of APAP remains largely unknown. Various hypotheses have been promoted and discarded or modified, as none have been fully explanatory to date.

Based on rodent and human pharmacokinetic studies, APAP has been long known to cross the blood-brain barrier. (Levy 2019) A 0.6 mg intravenous dose in rats achieved brain

concentrations that were 10–20% of blood levels. (Lambrecht 2006) A pediatric study administering 40 mg/kg acetaminophen via a nasogastric route reported a maximum concentration in the CSF of 15 lg/mL. (Anderson 1998) These and other studies indicate that a therapeutic dose of APAP achieves levels in the brain capable of analgesic and anti-pyretic actions.

APAP concentrated in fetal cerebrospinal fluid as compared to the adult brain in one study. Long-term (5 days) fetal exposure resulted in even higher transfer rates than short-term exposure. (Koehn 2019)

Whereas aspirin and other NSAIDS act via inhibition of prostaglandins, APAP does not. Neither does APAP effectively reduce inflammation in the clinical setting. For example, acetaminophen given orally at 100 mg/kg or intravenously at 100–300 mg/kg or intrathecally at 200 lg/kg reduced inflammatory pain but had no effect on edema in a randomized, double-blind, placebo-controlled trial. No significant improvement was seen in the APAP (1000 mg four times daily) group when assessed 2 and 12 weeks into treatment. (Alloui 2002; Brandt 2006; Case 2003)

To explain APAPs mechanism of action, the first pathway considered was Cox-1 and/or Cox-2 inhibition, the mechanism by which aspirin and NSAIDS work. Since APAP does not inhibit platelets and thus likely has no peripheral effect, the idea became that APAP may act on Cox-1/2 centrally. However, APAP does not affect 24-h body temperature elevation during the luteal phase of the menstrual cycle in humans, a process thought to be prostaglandin mediated. This suggests that APAP's effect on fever/temperature does not involve inhibition of prostaglandins (and so might not its analgesic effect). (Baker 2002) However, other studies contest this point. APAP may inhibit cyclooxygenase and thereby indirectly impact Cox pathways. APAP eliminates excessive peroxide tone caused by low-dose peroxynitrate, but not high-dose

peroxynitrate, via this pathway. (Schildknecht 2008) This finding may explain why APAP is effective only for mild-to-moderate, but not severe pain.

APAP also has direct effects on oxidative stress pathways (see below) and this may be a central mechanism of action.

A 2010 review in response to a joint meeting of three FDA advisory committees on the topic of the safe use of APAP concluded, "…paracetamol likely has a pharmacological mechanism that interacts with a variety of physiological pathways, likely within the central nervous system. As long as paracetamol's analgesic mechanism of action remains an enigma, assessment of its benefit/risk ratio…will be impeded". (Toussaint 2010)

Despite the absence of consensus on the mechanism behind APAP's analgesic action, it does have impacts on the inflammation and oxidative stress pathways that have been implicated in the genesis of ADHD.

Inflammation and oxidative stress

Inflammation has been suggested as a causal pathway for the genesis of ADHD. Moreover, oxidative stress and inflammation have a bidirectional relationship wherein each upregulates the other and their effects are mutually reinforcing. Generally, the developing embryo lacks a fully functional antioxidant defense system in early gestation so it is particularly vulnerable to irreversible damage from elevation of inflammatory pathways that, by definition, elevate reactive oxygen-nitrogen species. The brain lags behind other fetal organs and has been found to be more adversely affected in instances of oxidative stress. (Ornoy 2007)

Two systemic reviews/meta-analyses, Miyazaki (2017) and Schans (2017) examined links between ADHD and immune dysregulated diseases. Miyazaki (2017) evaluated studies enrolling more than 61,000 children (about 8,000 ADHD patients) and found that ADHD patients were more likely to have asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis in comparison to the non-ADHD subjects from the population. Similar results were found by Schans et al. (2017) in a systematic review and meta-analysis. They found a higher presence of asthma, eczema, and rhinitis in ADHD patients when compared to a control population.

ADHD has also been associated in some studies with elevations in peripheral blood cytokines, although the data are mixed. Pro-inflammatory cytokines can impact synaptic plasticity and neurogenesis and impact reaction time and working memory, both impaired in ADHD. Proinflammatory cytokines also modulate tryptophan and its metabolites, which, in turn affect dopamine. Lower tryptophan levels have been associated with the severity of ADHD symptoms. (Anand 2017)

In a systemic review of the literature, Anand et al (2017) found six studies assessing cytokine measurements in children with ADHD. Three of the reports found some elevations in cytokines among ADHD diagnosed children compared to controls but different cytokines were implicated in different studies. One study enrolled 21 medicated children (mean age 8.9) and found lower levels of IFN-γ and IL-13 and a lower TNF-α/IFN-γ ratio but no differences in these cytokines among non-medicated children. (Oades 2010) However, the authors found correlations between various pro-inflammatory cytokines and severity of ADHD symptoms such as inattention, hyperactivity, and opposition. In a study of 600 premature infants subsequently evaluated for ADHD at age 2, persistent or recurrent elevations of IL-6, TNF-RI, and IL-8 correlated with an increased risk of attention problems. (O'Shea 2014) A further 58 children with ADHD demonstrated significantly higher levels of IL-6 and IL-10 when compared to 36controls. Anti-Yo

antibodies, which have activity against Purkinje cells of the cerebellum, were also detected among 78% of children with ADHD but no anti-Yo antibodies were detected in controls. (Donfrancesco 2016) A final study measured cytokines in cerebrospinal fluid (CSF) of children with ADHD. More than half of children had detectable levels of IL-2, IFN-γ, TNF-B and IL-5. (Mittleman 1997) However, since no controls were available for comparison, the import of these findings is unclear.

Two studies evaluated auto-antibodies in ADHD children, both of which found higher immunoreactivity against anti-Purkinje cell antibodies. (Passarelli 2013; Donfrancesco 2016) Increased levels of antibasal ganglia antibodies and antibodies against the dopamine transporter have also been detected in ADHD, supporting the role of the immune system in the disorder. (Toto 2015; Giana 2015)

Data from several studies of genetic polymorphisms support the relationship between inflammatory cytokines and ADHD. (see Leffa et al. 2018 for a review)

Mothers with autoimmune diseases, particularly when those diseases are active in the prenatal period, have a higher risk of birthing children who will later be diagnosed with ADHD. Nielsen (2017) nested a case-control study within a large registry-linked birth cohort in New South Wales. Fully 12,610 children born from mothers with autoimmune diseases were compared to 50,440 controls. The outcome of ADHD was based on hospital registry diagnoses or pharmacy records of ADHD medications. Any type of autoimmunity was associated with a 30% increased risk for ADHD (RR 1.30, 95% CI 1.15–1.46). Several specific autoimmune conditions elevated the risk even further. These included diabetes mellitus (DM) Type 1 (RR 2.23, 95% CI 1.66–3.00); psoriasis (RR 1.66, 95% CI 1.02–2.70); and rheumatic fever (RR 1.75, 95% CI 1.06–2.89). The authors then conducted a meta-analysis wherein they added their own findings to

those of others yielding similarly significant (albeit somewhat reduced) associations. Risks for ADHD and any autoimmune disease were 1.20 (95% CI 1.30–1.38) based on two studies; DM Type 1 RR 1.53 (95% CI 1.27–1.85) based on four studies; psoriasis RR 1.31 (95% CI 1.10–1.56) based on two studies.

Similarly, Lee et al (2021) found significantly elevated risks between maternal autoimmunity and ADHD registry diagnoses in the Taiwan National Health Insurance database. Both a maternal diagnosis and a prenatal diagnosis yielded elevated risks for Sjogren's syndrome, ankylosing spondylitis, psoriasis, systemic lupus erythematosus, and psoriasis. Paternal autoimmunity did not impart an excess risk for ADHD. These strong and consistent findings are particularly relevant to the current discussion as they show that inflammatory diseases preceded ADHD, whereas other studies only show a concurrent relationship.

The above literature suggests that ADHD has an inflammatory component, that is, an inflammatory milieu preceding the onset of disease.

A compelling study has shown directly that oxidative stress biomarkers mediate an association between APAP and ADHD. Anand (2021) investigated whether the relationship between APAP exposure and ADHD is mediated by markers of oxidative stress using umbilical cord plasma. The authors used data from the Boston Birth Cohort, the same database used by Ji (2018, 2020). This has been described in detail above for those two studies. This analysis examined whether amino acids needed to synthesize the antioxidant glutathione and in the oxidative stress biomarker 8-hydroxy-deoxyguanosine may explain the association between cord plasma APAP concentration and ADHD. Covariates available for adjustment were maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, drinking during pregnancy, parity, maternal pre-pregnancy BMI, baby's sex, delivery type, gestational age,

birthweight, maternal fever during pregnancy, intrauterine infection/inflammation, and breastfeeding.

The diagnosis of ADHD was based on physician diagnoses in electronic medical records at a mean age of 9.3. Among 568 maternal-child pairs, cord unmetabolized APAP >50 percentile was associated with higher odds of an ADHD diagnosis after adjustment for covariates. (OR 2.10, 95% CI 1.43–3.11, p<0.001)

Cord unmetabolized acetaminophen was positively correlated with methionine (R = 0.33, p< 0.001), serine (R = 0.30, p< 0.001), glycine (R = 0.34, p< 0.001), and glutamate (R = 0.16, p< 0.001). With each increase in cord 8-hydroxy-deoxyguanosine, methionine, serine, and glycine levels, ADHD risk increased. Adjusting for covariates, cord methionine statistically mediated 22.1% and glycine mediated 22.0% of the association between cord acetaminophen >50th percentile with ADHD.

Acetaminophen's metabolism as an initiator of inflammatory/oxidative stress cascades works as follows. APAP is mainly excreted following conjugation with glucuronic acid (reduced glutathione or GSH) or sulfate. About 90% is rendered non-toxic by this pathway. A variable fraction, however, is oxidized in the liver by several CYP450 isoforms (CYP2E1, CYP1A2, CYP3A4, and CYP2A6) to NAPQI. NAPQI is a highly reactive compound that covalently binds to thiol groups within proteins and lipids and triggers oxidative stress. When reduced glutathione (GSH) is depleted, it cannot take the catalysis down the elimination pathway that results in the "safe" compound L-cysteinyl S-acetaminophen. Instead, if concentrations of NAPQI exceed the available GSH, NAPQI initiates a mitochondrial cascade that leads to accumulation of reactive oxygen species, formation of peroxynitrite, mitochondrial membrane permeability transition, and ultimately cell death. (Jaeschke 2021)

NAPQI is also generated in the brain by the CYP450 isoform CYP2E1. (Upadhya 2000) CYP2E1 is present in the fetal brain as early as 15 weeks of gestation, and significant heterogeneity of CYP2E1 in various regions of the brain. (Allen Institute, 2019, available at https://www.brainspan.org/lcm/search?exact_match=false&search_term=%22CYP2E1%22&search_type=gene)

As NAPQI is covalently bound to GSH, it depletes GSH in the brain and has been shown to aggravate oxidative stress. In rats, cortical neuronal death involving Cytochrome C release and caspase 3 activation is induced by paracetamol at doses below those required to produce hepatotoxicity. (Posadas 2010)

Acetaminophen hepatotoxicity is thought to be the result of NAPQI production. NAPQI is a unique toxic moiety resulting only from APAP metabolism. No other known product produces NAPQI. Low doses of APAP NAPQI are neutralized by glutathione but at higher doses, glutathione is overwhelmed and NAPQI is produced in large enough amounts to cause liver damage. More recently, the finding that NAPQI is generated in the brain raises the possibility that cortical inflammation and oxidative stress may play a role in abnormal neurodevelopment.

The strong link between inflammation/oxidative stress and ADHD, reviewed above, argues for the hypothesis that APAP, particularly in that when used by a pregnant woman over longer duration, APAP depletes glutathione and produces NAPQI in the fetal brain. This, in turn, among susceptible individuals, triggers ADHD. The Anand study, demonstrating oxidative stress markers in the relationship between APAP and ADHD, provides direct evidence for this hypothesis.

Both animal and human studies show that APAP causes oxidative stress. Oxidative stress perturbs the underlying mechanisms that occur in normal neurodevelopment. While the liver is capable of repairing oxidative stress as a regenerative organ, the same is not true for embryonic or neurodevelopmental cells and tissues. Oxidative stress affects cell proliferation, differentiation, apoptosis and necrosis (Dennery 2007). All of these processes operating in normal balance with one another are crucial to neurodevelopment.

Overall, there is evidence to support several mechanisms by which APAP may lead to disruption of normal neurodevelopment. Baker (2020) demonstrated that APAP is linked to neuroanatomic defects seen with ADHD. A plethora of data suggests that the mechanistic pathway creating this association is via triggering inflammation/oxidative stress. Abnormalities in inflammation and oxidative stress are apparent in children with ADHD. APAP metabolism can interfere with these pathways, particularly when taken in high doses or over longer time periods. Direct mediation by oxidative stress biomarkers has been demonstrated in cord blood. Further research must be done to fully appreciate these links but there is ample current data to support biologic plausibility.

I put moderate weight (somewhere in between consistency and specificity) on the criterion of biologic plausibility in that, as Bauer noted, animal studies are not subject to bias and confounding, but extrapolating from animals to humans is fraught because animals are not humans. On the other hand, biologic plausibility only requires plausibility, not establishment of biologic pathways. Thus, my weighting was neither heavy nor little weight, but somewhere in between. Based on the above, the criterion for biologic plausibility is met.

Analogy

According to Rothman, “Analogy refers to drawing inferences about the association between a given exposure and disease based on what is known about other exposure-disease relations. For example, based on what is known about the health effects of cigarette smoking, we might expect that inhalation of other combustibles (e.g., marijuana) would have similar effects, even in the absence of studies on the subject.” (Rothman 2008 p 21)

This criterion strengthens the case for causality but is not required for causality. As per Bradford Hill, “With the effects of thalidomide before us, we would surely be ready to accept slighter but similar evidence with another drug . . . in pregnancy.” But sometimes drugs that are expected to act similarly—even drugs within the same class of medications—have disparate effects. Meanwhile, there are often causal relationships that exist in the absence of obvious analogies, because whether an appropriate analogy exists “is limited by the breadth of knowledge and imagination of the scientist” and not necessarily “the falsity of the [causal] hypothesis.” (Rothman 2008, p 22). Thus, finding a drug that works through the same putative biologic mechanism as APAP and is established to cause ADHD would strengthen the case for APAP causing ADHD, but its absence would not substantively detract from a causality determination.

There is a relevant analogy for APAP and ADHD. Valproic acid has been established to cause ADHD when taken in pregnancy. As the Court noted in its order, the DSM describes valproic acid as a risk factor for neurodevelopmental disorders (Order at 13), and the valproic acid label specifically states that valproic acid likely causes ADHD.

The mechanism of teratogenic action for valproic acid is believed to be oxidative stress, the plausible mechanism detailed above. This is the same mechanism by which lead is thought to cause teratogenicity. (Diav-Citrin 2008) Al-Amin (2015) injected mice with 600 mg/kg valproate

during pregnancy and observed significant alterations in antioxidants, including increased levels of malondialdehyde (MDA), nitric oxide (NO), advanced protein oxidation product (APOP) and decreased glutathione (GSH), catalase (CAT) and sodium dismutase (SOD) activity. Other investigators have reported valproic acid as pro-oxidative in humans, animals and cultured cells (Ornoy 2023)

One large cohort study linked prenatal valproic acid use, but not other anti-epileptic medications, to ADHD risk. In a population-based cohort study of 913,302 live-born children representing all singleton births in Denmark (1997-2011), prenatal exposure to anti-epileptics including valproate, was obtained from the Danish National Prescription Registry. Children diagnosed with ADHD or redeeming a prescription for ADHD were identified from a central psychiatric disease registry. The cohort was followed up from birth until 2015 (median age at end of study 9.4 years). A total of 580 were identified as having been exposed to valproate during pregnancy. Children with prenatal valproate exposure had a 48% increased risk of ADHD (adjusted HR 1.48; 95% CI, 1.09–2.00) compared with children with no valproate exposure. The association was independent of maternal psychiatric disorders, maternal epilepsy, maternal diabetes, maternal age, sex, year of birth, and parity, and after excluding women who smoked during pregnancy. No associations were found between other anti-epileptic drugs and ADHD. (Christensen 2019)

Two other cohort studies have shown ever more accentuated risks but did not find statistical significance. In a pooled in a meta-analysis by Veroniki (2017), only two studies met their inclusion criteria in measuring valproic acid and ADHD. Both showed positive relationships ranging from 1.51–2.84. Both reported very wide confidence intervals around estimates reflecting small sample sizes, use of behavioral measures, and for the study estimating the risk

of 1.51, exposure defined by valproic acid plus another anti-epileptic drug. Thus, the Danish estimate, with its more modest result of HR 1.48 likely more accurately represents the true risk.

That risk is of similar magnitude to the risk for fetal exposure to APAP and ADHD. As discussed under Strength of Association, risk estimates have typically been 1.2–1.6.

Because analogy is rarely met, it is generally considered to carry limited weight in asserting causality. Nevertheless, it strengthens the argument for causality.

I put little weight on the criterion of Analogy. In the situation of APAP and ADHD, based on the above considerations, I considered the tenet of Analogy to be met.

Specificity

The definition of specificity, according to Rothman (2008) is as follows. “In Hill’s formulation, specificity of an association can refer either to a cause having a single effect or an effect having a single cause.”

Although it might appear that there are cases wherein an exposure causes a single disease, such as the case for asbestos exposure and mesothelioma, in fact, that is not true. Asbestos is associated with several cancers including cancers of the gastrointestinal tract. (Kim 2013) Moreover, other mineral fibers such as erionite, fluoro-edenite, and probably balangeroite can induce mesothelioma, as can therapeutic radiation for other malignancies. (Attanoos 2018) Even teratogens such as thalidomide, which is often considered to specifically cause limb malformations, in fact also causes congenital defects of the ear, heart, and other internal organs. (Kim 2011)

Indeed, as Rothman's textbook *Modern Epidemiology* notes, it is rare to find a truly specific relationship. Therefore, epidemiologists uniformly put little emphasis on the criterion of specificity. Bradford Hill, himself, cautioned against relying too much on this criterion—"we must not, however, over-emphasize the importance of the characteristic"—and there are numerous examples where it is not satisfied, including the association between tobacco and lung cancer: not all smokers get lung cancer, and some get lung cancer even though they have never smoked.

I put little weight on the criterion of Specificity. I believe that the criterion of specificity is not met.

Biological gradient (dose-response)

Biologic gradient, also termed dose-response means that the greater the exposure, the greater risk of disease." In the words of Bradford Hill, "the fact that the death rate from cancer of the lung rates rises linearly with the number of cigarettes smoked daily adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers." The Court in its order agreed with this: "a dose-response relationship is strong but not essential evidence of causation." (Order at 56).

Various association studies have assessed duration, frequency, and concentration of APAP use in relation to ADHD. Longer durations of use, more frequent use as measured by greater number of trimesters of APAP use, and higher concentration (in meconium, cord blood and maternal blood) demonstrated biologic gradients. I considered the Baker (2020) study to be most informative regarding this criterion. The Court determined that Baker is a well-respected study because it employed a direct measure of APAP via meconium. I concur in that meconium concentrated APAP cumulatively in the final two thirds of pregnancy.

Comparing fetal meconium with recall for exposure to APAP, Laue (2018), using data from the GESTation and Environment (GESTE) study, recruited 238 pregnant women during their first trimester and assessed APAP use at recruitment as a yes/no question and also exposure during labor using medical records. Meconium was measured using ultra performance liquid chromatography tandem mass spectrometry. Acetaminophen administration during labor was associated with a significant increase in meconium APAP concentration (p=0.0002). However, self-reported intake during pregnancy was only marginally associated with meconium concentrations (p=0.10), adjusting for administration at delivery. This demonstrates that ever/never report of APAP was substantially misclassified as a metric for use over the course of the full pregnancy. Self-report in early pregnancy resulted in a substantial underestimate of later exposure. This may be because of forgetting or considering inconsequential an OTC medication or because use varied over time. Whatever the explanation, recall was a less valid measure and one that would underestimate the true effect size.

Baker found that the risk of developing ADHD increased monotonically with increasing concentration of APAP in fetal meconium. High levels of APAP detected in meconium increased the odds of ADHD more than 4-fold (OR, 4.10; 95% CI, 2.41–6.95). With each doubling of exposure, the odds of ADHD increased by 10% (OR, 1.10; 95% CI, 1.02–1.19). This clearly demonstrated a dose-response.

Ji (2020) also used a biomarker that reflects what the fetus was directly exposed to: cord blood. Compared with being in the first tertile, being in the second and third tertiles of cord APAP was associated with higher odds of ADHD diagnosis (OR for second tertile, 2.26, 95% CI 1.40–3.69; OR for third tertile, 2.86, 95% CI 1.77–4.67). Again, this demonstrates a dose-response, but the metric is limited as it measures only short-duration exposure.

Similarly, Ji (2018) used maternal blood to measure APAP exposure in relation to ADHD risk. Compared to unaffected children, the authors reported a significant positive dose-response association with ADHD diagnosis for this maternal APAP biomarker after adjusting for indication of APAP use and other pertinent covariates. Compared to levels in the non-detection category, below median and above median levels of maternal APAP were associated with a 58% and 88% increase in the odds of ADHD diagnosis, respectively (OR below median 1.58, 95% CI 1.02–2.46); OR for above median 1.88, 95% CI 1.18–3.00).

Using maternal report, Liew (2014) showed that APAP use during pregnancy for 1 week, 2.5 weeks, 6-10 weeks, 11-20 weeks, and >20 weeks, as compared to no use, yielded RRs of 1.18, 1.29, 1.49, 1.24 and 1.53, respectively, as well as a statistically significant trend. Exposure response trends were found with increasing duration resulting in higher risk estimates for all outcomes (i.e., hyperkinetic diagnosis, ADHD medication use, and ADHD-like behaviors; p trend < 0.001). Among women reporting use of 20 or more weeks of APAP, risk for a child receiving a hyperkinetic diagnosis almost doubled (hazard ratio, 1.84;95% CI, 1.39–2.45) and the risk for receiving ADHD medication increased by 50% (hazard ratio, 1.53; 95% CI, 1.21–1.94).

Ystrom (2107) similarly found that the RRs for APAP use for 1-7 days, 8-14 days, 15-21 days, 22-28 days, and ≥29 days were 0.90, 1.18, 1.35, 1.60, and 2.20 respectively. Again, these estimates reflected a statistically significant trend. Inoue (2021) reported increasing risk with more weeks of use. For 1-5 weeks, 6-10 weeks, and >10 weeks the RRs were 1.07 (0.92–1.23), 1.27 (0.95–1.70), and 1.32 (1.06–1.63), respectively.

Ystrom (2017), looking at dose-response from the perspective of weeks used (frequency), demonstrated that the more trimesters in which APAP exposure occurred, the larger the risk. Ystrom reported that one trimester of use resulted in a RR of 1.07 (95% CI 0.96–1.19), whereas

two trimesters yielded RRs of 1.34 (0.77–2.34) (first and third), and 1.63 (1.28–2.07) (second and third). Liew (2014) similarly showed that use in the first and second trimester yielded a RR of 1.09; second and third trimester, RR 1.39 and three trimesters, 1.44. APAP use during pregnancy for 1 week 2.5 weeks, 6-10 weeks, 11-20 weeks, and >20 weeks, as compared to no use, yielded RRs of 1.18, 1.29, 1.49, 1.24 and 1.53 respectively.

Overall, although fewer studies examined dose-response relationships than did those relying on ever/never use of APAP during pregnancy, those that did found that longer duration use, greater frequency of use, and greater concentrations of APAP metabolites resulted in the highest risks. In its order, the Court noted that a "key issue" was that "none [of the studies] were able to record the actual dosages taken by pregnant women." (Order at 90) I agree that actual quantitative doses (in terms of milligrams) were not recorded. But respectfully, this is not required for scientists to reach a conclusion on dose response. Like so many other aspects of my analysis, the literature is best assessed not based on a single assessment of dose but instead on a totality of the data. Classically, dose is defined by duration times amount and none of the studies measured the totality of dose. At the same time, the findings that higher concentration (representing amount), longer duration, and more frequent use all consistently increased risk, in aggregate argue strongly for a dose-response relationship. Indeed, in the absence of a combined measure of dose, each of these would be expected to underestimate true risk. In the field of epidemiology, it is common for scientists to evaluate dose response based on days of exposure, weeks of exposure, or other proxies for quantitative dose in milligrams. To take just one example (of many), when evaluating the studies assessing the connection between chemical-contaminated water and various diseases at Camp Lejeune, the U.S. Government's ASTDR causality assessment considered "some of the viewpoints associated with [Bradford] Hill," including "exposure-response." When evaluating exposure response, however, the government analysis (as here) did not have access to precise quantitative measures of the

various chemicals to which the soldiers at Camp Lejeune had been exposed. They instead (as here) relied on the number of days, weeks or months of exposure when evaluating dose response. Indeed, they employed this kind of exposure-response analysis numerous times when evaluating several of the chemical-disease relationships. (ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases (January 13, 2017)). ASTDR employed a similar methodology just last month when evaluating the link between the water at Camp Lejeune and various cancers, i.e., ASTDR employed "duration of assignment" and "duration of employment" at Camp Lejeune "as a surrogate for overall cumulative exposure" to the relevant chemicals. (Bove, et al., Evaluation of Cancer Incidence Among Marine and Navy Personnel and Civilian Workers Exposed to Contaminated Drinking Water at USMC Base Camp Lejeune: A Cohort Study (Jan. 29, 2024).

That is how I analyzed this factor, as many authors here did as well. The authors of Liew (2014), for example, noted that "weeks of use (1, 2–5, 6–10, 11–20, >20 weeks) were used to examine exposure" response and on that basis "found exposure response trends with increasing frequency of use during gestation." The authors of the Ji (2018 and 2020) and Baker (2020) studies employed biomarker data that similarly allowed for a comparison of disease rates at different levels of exposure. Just as there was nothing improper about the U.S. Government evaluating dose-response in that way, it was epidemiologically valid for these study authors to employ a similar methodology in the absence of finer-grained data on quantitative dose at the level of milligrams.

I am aware that some of the dose-response curves were not linear; there were outlier estimates (e.g., Chen 2019). However, this is to be expected given small sample sizes and wide confidence intervals. Since many of the confidence intervals overlapped, indicating no statistical difference between tertiles of duration, I considered trends more important than any single

estimate. The trends uniformly showed duration-response relationships. Indeed, many of the study authors explicitly interpreted their results as evidence of a dose-response relationship. (Liew 2014, Ricci 2023, Baker 2020, Ji 2018, Ji 2020, Alemany 2021)

In accord with the Court's conclusion that, "a dose-response relationship is strong but not essential evidence of causation," (Order at 56), I weighed biologic gradient heavily in my determination of causality. I find that the criterion of biologic gradient is met.

Temporality

"Temporality means that a cause must precede its effects, and this is a necessary condition for valid causal inference." (Rothman 2008, p 20) That is, the exposure must precede the outcome in time: "which is the cart and which the horse?" (Hill 1965) In most circumstances, I would consider temporality to be met simply in that almost all studies in the epidemiologic literature on APAP and ADHD have been prospective cohorts. In this design, mothers were asked about exposure either during pregnancy or shortly after birth. Outcomes were assessed months or years later.

However, the Court's Order stated that "a reliable assessment of the temporality factor would engage with the fact that it is not currently known when… ADHD develop[s] in the fetal brain, and with the possibility that some studies measured acetaminophen use either before or after the development window." (Order at 88)

For APAP, as noted above, the greatest risk appears to be in the third and possibly second trimester of gestation. For the effect to precede the cause, we would have to posit that the sensitive period of neurodevelopment occurs in the first or second trimester. In fact, in the case

of teratogens, the exposure must be present during the time the developmental process of interest is taking place.

The questions are then three-fold. First, what is the anatomy and physiology of brain impairments seen in ADHD? Second, when during gestation are these areas and functions in the brain developing? Third, given the timing of neurodevelopment of the parts of the brain relevant to ADHD, is there any possibility that disruption prior to the third trimester could cause ADHD – that is, is it plausible that the cart came before the horse?

Regarding the first question of what the most important brain structures are involved in ADHD, most authors agree the answer, at least in good part, is the prefrontal cortex. (Hinshaw 2018)

ADHD involves operations termed “executive functions” coordinated by the prefrontal cortex. The executive functions mediated by the prefrontal cortex that are central to the impairments seen in children with ADHD include the organization of input from diverse sensory modalities, the maintenance of attention, the monitoring of information in working memory, and the coordination of goal-directed behaviors (Jurado and Rosselli 2007, Miller 2001, Miller and Cohen 2001) Neuroimaging research demonstrates that individuals with ADHD show intrusions of daydreaming neural networks when attention-focused networks should be engaged. (Raichle and Snyder 2007) More subtly, one study showed that youths with ADHD-related symptoms, rather than daydreaming or mind-wandering per se, displayed a blank thought pattern during attentional lapses. (Van den Driessche 2017). As a result, difficulties with remembering, sequencing, time management, and organizational skills characterize many individuals with ADHD.

Although many areas of the brain are involved, as demonstrated by an elegant recent neuroimaging study by Gehricke (2017), the prefrontal lobe is particularly affected. The authors note, “findings revealed significant associations between ADHD diagnosis and widespread changes to the maturation of white matter fiber bundles and gray matter density in the brain, such as structural shape changes (incomplete maturation) of the middle and superior temporal gyrus, and fronto-basal portions of both frontal lobes.” Gehricke (2017)

Thus, the brain location of greatest interest with respect to development of ADHD is the prefrontal lobe. This brings us to the second question of when during brain development, the prefrontal lobe is most sensitive to disruption. A simple answer is the end of the second and third trimesters of pregnancy.

Central nervous system formation begins shortly after implantation with the rapid expansion of cell layers and their formation into a crude, embryonic notochord. At the cranial (head) end, the number of neurons increase rapidly and their number peaks in the early second trimester, between week 13 and 16 of gestation. (Kolk 2022) After assuming their final position, neurons begin to differentiate to form synaptic connections.

Throughout the mid-second and third trimesters and in the few weeks after birth (between 17 and 50 weeks of gestation), pyramidal neurons and interneurons within white and gray matter mature and differentiate. (Kroon 2019, Petanjek 2008) Dendritic length increases and spines will develop, reaching out to other cortical and subcortical targets. This is the case for both excitatory and inhibitory networks, both of which mature extensively in terms of their anatomy and their network properties.

The chief landmarks in the brain are its sulci, which appear as linear indentations. In the prefrontal lobe, the most evolutionarily advanced center of executive function, the primary sulci (superior frontal, inferior frontal, and precentral), develop during the very end of the second trimester (gestational weeks 25–26). (Teffer 2012) During the third trimester, from weeks 26 and beyond, the various layers of the brain continue to mature, as spines develop, basal dendritic length increases, and interneurons differentiate. This rapid phase of synaptogenesis involves first, an accumulation of synapses and then, a process called pruning or refinement of synaptic connections, the removal of unused synaptic contacts. (Huttenlocher 1990)

Thus, the most sensitive period of prefrontal neurodevelopment is in the mid-second and third trimesters when neurons and synapses are growing and differentiating into a functional organ. As gestation progresses, structures become more sophisticated and more functional in their capability to send signals and to interact internally. (Kolk 2022)

In answer to the third question of whether the critical neurodevelopmental window for ADHD genesis might be during the first and/or early second trimester is that this supposition would be inconsistent with the biology and toxicology of fetal brain development. During that time, the cells bound to become neurons are in their most emergent form. They have not reached the point of functionality in terms of number, shape (dendrites), location, nor connectiveness. During the first trimester, the prefrontal lobe has not even begun to develop. Because they are so early in embryonic development, toxicants would cause extreme disruption in the form of structural congenital defects.

First trimester toxicants cause major, anatomically apparent malformations. Folic acid deficiency in the first trimester, for example, results in neural tube defects and if severe, anencephaly (absence of brain tissue). (van Gool 2018) Thalidomide toxicity, which resulted in extreme limb

malformations, occurred only during gestational days 35-50 (5-7th week) when the limbs were in their earliest stage of development. (Kim 2011) Vitamin A excess in the first trimester causes noticeable structural abnormalities of the face, brain, and heart such as cleft lip, cleft palate, hydrocephalus (cranial enlargement due to excessive fluid around the brain), and major heart malformations. (Rothman 1995, Bastos 2019)

Thus, it is unlikely that ADHD develops before the time in pregnancy when APAP is associated with ADHD. Indeed, the timing of prefrontal lobe development is concordant with the timing of the sensitive window for APAP toxicity – a requirement of developmental toxicity. The prefrontal cortex is at a peak of development during the late second and third trimesters. Interruption of development during that sensitive window would be expected to lead to functional impairments seen in ADHD.

APAP appears to have its greatest impact during the second and/or third trimester. APAP use in the first trimester produced RRs of 1.09–1.31 and in the second trimester, 1.13–1.20. (Ystrom 2017, Chen 2019, Inoue 2021, Stergiakouli 2018). In contrast, APAP use during the third trimester (Liew 2014, Ji 2018, Gustavson 2019, Baker 2020, Ji 2020) ranged from 1.28–2.86. In the third trimester, use of APAP was associated with ORs of 1.88–2.86 in four of five studies. Thus, APAP exposure (the cause) and impaired neurodevelopment (effect) are cotemporaneous. As with other toxicants that cause teratogenicity (reviewed above), the cause does not precede the effect.

In keeping with the admonishments of Rothman and Hill that *"*a cause must precede its effects, and this is a necessary condition for valid causal inference," I put great weight on the tenet of temporality.

Based on the above, in my assessment, the criterion of temporality is met.

Coherence

This criterion addresses the overarching question of whether the hypothesized causal relation "conflicts with current understanding of the disease process." (Rothman 2008) It considers the totality of the literature. It is not a question of whether the cause creates an effect, but rather the counterfactual of whether the cause-and-effect relationship conflict with epidemiologic and biologic understanding.

It would be redundant to repeat all that has been said in this report thus far, but in sum, I have opined that exposure to APAP is associated with a modest yet consistent association that demonstrates a dose-response and occurs during the critical window when teratogenesis relative to ADHD is most relevant. In my determination, APAP exposure is analogous to another known neurotoxicant (valproic acid) that causes ADHD. There is a biologically plausible explanation for the APAP and ADHD relationship. Thus, the epidemiologic and biologic literature do not conflict with the possibility that APAP use during pregnancy causes ADHD.

Because coherence is subject to false positives (i.e., there are hypothesized causal relations that are coherent with the disease process but are not necessarily causal), I placed low weight on this tenet.

Still, I believe that the criterion of coherence is satisfied.

Experiment

The type of experiment that Hill had in mind was a natural experiment in which an exposure changes population-wide and the researcher evaluates whether disease rates change. He

indicated that such natural experiments rarely occur in an informative manner and he placed little weight on this tenet. The natural experiment approach, generating an ecologic analysis, is not discussed here because studies that assess risk at the population, rather than the individual level suffer from a plethora of biases and are generally considered by epidemiologists to be relatively uninformative. However, in rare cases, such as, for example, when a medication is abruptly removed from the market, such data can prove supportive. Such has not occurred in the situation of APAP.

The modern approach, which is considered to be highly useful, is a randomized clinical trial in which individuals are assigned by the researcher to an exposure (APAP) group. The benefit of experimental studies (randomized clinical trials) is that because they allocate exposure randomly between groups, they avoid a good deal of confounding and bias. However, randomized clinical trials of APAP use in pregnant women are unethical. It would be unethical to ask non-using persons to use the medication to determine if it is hazardous to their fetuses. This is particularly true since observational data suggests that such exposure may be hazardous to the unborn child. An alternative design would be to require women already taking APAP for fever or pain to entirely avoid usage. This would, again, be unethical since APAP may be an appropriate treatment for certain conditions in pregnancy including fever. Indeed, it is the only medication recommended for this indication during pregnancy. Denying its use would potentially put fetuses at risk of damage from uncontrolled fever.

Another experimental approach that is used to support epidemiologic evidence is animal experiments in which all parameters except exposure (APAP administration) are kept constant. The results of such experiments have, to a great degree, supported the link between APAP and ADHD (reviewed above). But I am unwilling to find this tenet satisfied based only on experiments in animals.

Since conduct of a randomized clinical trial in humans does not exist, is out of the question for future conduct, and thus cannot add or detract from the other Hill causality tenets, I placed low weight on the criterion of experiment. Experiment is, by definition, not satisfied.

Systematic error

A ubiquitous concern about reliance on observational studies to make causal inference—i.e., to determine that APAP causes ADHD—is the possibility that error, in the form of bias or confounding, is responsible for observed associations. Bias and confounding must be minimized as the drivers of observed study associations. Moreover, the literature must be evaluated for the possibility that associations occurred by random chance.

Bias

Cohort studies are less affected by bias than case-control studies. Nonetheless, the effect estimates linking APAP to ADHD have almost surely been impacted by selection and misclassification bias—the questions are the direction the bias runs and its magnitude. Masarwa analyzed their meta-analysis results taking into consideration both bias and confounding effects. Correction for exposure misclassification resulted in an increase in the adjusted RR of about 45%, meaning that without adjustment, bias diminished the observed effect by 45% as compared to a true value. Correction for confounding resulted in a maximum decrease of 19% (confounding was inflating the observed effect). Thus, the two spurious effects were in opposite directions, with exposure misclassification having the greater impact, i.e. even after accounting for both, the result would be a greater bias toward the null. This suggests an underestimate of the true effect.

Summarizing earlier topics in this report, selection bias affected the two largest cohorts analyzed regarding prenatal APAP use and ADHD, the Danish National Birth Cohort (DNBC) and Norwegian Mother and Child Birth Cohort (MOBA), due to selective participation and selective dropping-out. DNBC enrolled only 31% of eligible women and MOBA had only a 40% response rate. As compared to the Norwegian population at large, Nilsen et al. (2009) found that those enrolled in MOBA were less likely to be young (<25 years), smokers, and to have had adverse birth outcomes in the past and were more likely to use multivitamins and folic acid supplements. This suggests participation among a healthier than average group of women. It would have affected generalizability although not necessarily internal cohort comparisons. Nonetheless, it suggests that in the population overall, the impact from APAP exposure may be larger than expected from the results of studies.

MOBA also experienced high drop-out rates (40%), which almost surely would have impacted risk estimates. DNBC, as well, suffered from a substantial proportion of missing data. About 30% of participants missed one or more telephone interviews. Since women willing to enroll in MOBA were healthier, it is likely that those who remained in the study had similar health characteristics. The same was probably true for DNBC. Healthier women are less likely to have a child with ADHD and less likely to use APAP. Potential risk factors for ADHD include smoking, a history of pregnancy complications, depression/anxiety, and genetic predisposition. Long-duration APAP users also tended to be smokers, obese, and have more depression and anxiety. The paucity of such women remaining in both MOBA and DNBC would have led to underestimates of true effect sizes.

In addition to selection bias, misclassification is a serious concern throughout the literature on APAP use in pregnancy and ADHD. Since many women do not consider acetaminophen to be a medication, recall of exposure was underestimated. Questions that specifically asked, “Did you

take acetaminophen?" would have more likely captured exposure than those asking about the use of any medications or about the use of medications for specific indications. In DNBC, exposure assessment of analgesics was queried with the question, "did you take pain killers?" If yes, the respondent chose from a list of 44 medications, including APAP. Analgesic use was asked for each week of pregnancy so that both timing and duration could be calculated. In MOBA, APAP exposure was queried in any woman reporting headache, fever, cold, or backache. Among such women, medication use was asked in an open-text format. Although these questions were more directed than simply asking about any medication use, women still may have considered APAP as not "a pain killer" or as too inconsequential to mention for indications. Many of the other cohorts in this literature were not even this specific in their queries about analgesics. Overall, this almost certainly led to systematic underreporting by both women whose children were bound to develop ADHD and among those whose children were not. This would have resulted in non-differential misclassification and a bias toward the null, i.e. an undervaluation of the risk.

Beyond the problem of naming APAP as an exposure, studies generally categorized use as ever/never. Such studies aggregate pregnant women with long duration and/or high dose use of APAP with women only minimally exposed to APAP. Laue (2018) found that a yes/no question on pregnancy APAP use correlated poorly, whereas APAP administration during labor and delivery correlated highly with neonatal meconium levels. As meconium is considered a valid measure of toxicant concentrations during the second two thirds of pregnancy, (Baker (2020), Ostrea (2006), Delano (2019), Lange (2014)), this suggested that recalled ever/never exposure underrepresented true effect. Since women exposed for longer duration or in more trimesters had the highest risk of an ADHD affected child, ever/never use data underestimated true effect sizes.

Although many studies enrolled women in the second trimester of pregnancy, those that enrolled women later or had fewer interviews during pregnancy would have poorly captured changes in behavior over time. Again, this admixed women with different exposure patterns and resulted in bias results toward the null.

Other “hard” exposure ascertainment methods may have resulted in similar or even worse misclassification. Pharmacy records underreport APAP exposure since they typically do not capture OTC sales. Cord and serum blood measured APAP concentrations only when exposure occurred within the preceding 48 hours or so. If hospital protocol was to administer APAP during labor, the relationship to earlier patterns of APAP use would have been voided. These considerations would uniformly have led to misclassification toward the null since inaccurate exposure assessment would have affected offspring developing ADHD equally to those not - outcome was unknown at the time of APAP exposure assessment.

Registries only collect data on children that seek medical attention and thus, presumably have more severe disease. Again, such measures would have biased observed results toward the null and underestimated true risk.

The Masarwa (2020) result that bias in their studies diminished observed risks, then, is in keeping with what would be expected. Studies based on biologic measures such as maternal blood, cord blood, and meconium have reported larger risk estimates than those based on self-reports. Registry-based outcome studies have shown larger effects than those based on parental behavioral assessments. These findings support concerns that much of the literature on APAP-ADHD underestimates true risk.

Confounding

As the Court noted, “two major potential confounders are at issue in this litigation: confounding by indication and confounding by genetics.” (Order at 20) I agree this is a critical point, and I take it with all seriousness. Therefore, I have extensively considered the possibility that one or both sources of confounding may explain the literature linking APAP pregnancy use to ADHD risk.

The potential for confounding by indication and genetics are detailed above. I will summarize these here.

Confounding by indication

Fever is an indication for APAP use and has been linked to ADHD. This suggests that fever might artificially elevate observed risks. The possibility that fever may confound the relationship between APAP pregnancy use and ADHD is particularly important to consider since APAP is currently the only recommended analgesic for control of fever throughout much of pregnancy. However, the link between fever and ADHD as an explanation for the APAP-ADHD association is unlikely for the following reasons.

First, the literature suggesting that fever is associated with ADHD is primarily limited to two cohort studies (Dreier 2015, Gustavson 2019) and is thus far less robust than the literature linking APAP exposure to ADHD. The association between fever and ADHD risk was only observed in the first and perhaps second trimesters. In contrast, use of APAP appears to have its greatest impact on neurodevelopment in the third and possibly second trimester as reviewed above. (Ystrom 2017, Chen 2019, Inoue 2021, Stergiakouli 2018, Liew 2014, Ji 2018, Gustavson 2019, Baker 2020, Ji 2020, rodent model sensitive window Philippot 2017)

Second, only one cohort study (Gustavson 2019) found a risk from fever after adjustment for APAP use.

Third, confounding by fever in the relationship between APAP and ADHD has been considered after adjustment in multivariable models, after stratification of febrile/non-febrile women, as well as after excluding women with fever or infection. These techniques did not change the findings of observed, positive and statistically significant associations between APAP and ADHD (Liew 2016, Ystrom 2017, Ricci 2023). If anything, there is some suggestion that fever interacts with APAP use such that APAP exposed fetuses also exposed to maternal fever have a particularly elevated risk of developing ADHD. Ystrom (2017) found that APAP use for fever and infections for duration of use between 22 to 28 days was associated with a particularly high risk of ADHD (HR 6.15; 95% CI 1.71–22.05), suggesting a potential interaction. Similarly, Ji (2018) reported that mothers with a prenatal infection had an APAP use OR of 2.81 versus the 1.57 OR for APAP use without infection.

Fourth, fever is an uncommon indication for long duration APAP use, the most concerning type of exposure given its greater strength of association to ADHD. Long-term APAP use is mostly used for pain. Vlenterie (2016) showed that indications for >28 days of APAP use in MOBA were headache or migraine (80.2%), back pain and pelvic girdle pain (66.0% and 49.9%, respectively), and fever (24.9%). Based on acetaminophen diaries, Bandoli (2020) found that women using APAP for more than 20 days reported that they used it mostly for headache (52%). Use was less common for pain or injury (27%). For cold or flu the proportion reporting APAP use was only 13% and fever only 4%.

This raises the question of whether pain may be an indication that confounds the APAP-ADHD relationship. There is essentially no evidence that pain during pregnancy (headache, backpain,

etc.) increases the risk of a child being diagnosed with ADHD. Liew (2016), Masarwa (2020), Brandlistuen (2013) and Inoue (2021) adjusted for painful conditions in multivariable models and found no indication of a reduction in the observed association between prenatal APAP use and ADHD or ADHD-associated neurodevelopmental symptoms.

Similarly, concomitant use of NSAIDS has not been shown to impact risk of ADHD or ADHD-associated neurodevelopmental outcomes. Brandlistuen (2013) found no association between Ibuprofen and these outcomes. Havdahl (2022), in a genetic risk score study, did not detect any relationship between genetic risk for ADHD and Ibuprofen. In APAP analyses, adjustment for use of aspirin or Ibuprofen had no impact on risk estimates. Liew (2016) adjusted for aspirin and ibuprofen and found no change in results. Ruisch (2018) showed no change in the relationship between teacher assessment of ADHD and oppositional disorder scores after adjustment for other analgesics. Tovo-Rodriguez (2018), similarly found no impact of adjusting for NSAIDS. Thus, there is no consistent evidence of confounding by NSAID use.

Ricci in the most definitive study to date, a comprehensive meta-analysis of all literature as of 2022, excluded confounding by indication as having any substantial impact on the risk from APAP use. Moreover, the facts that 1) long-term APAP is rarely used for the indication of fever, 2) the different timing of fever sensitivity and APAP sensitivity, 3) the limited data showing that fever increases ADHD risk after adjustment for APAP, 4) the multiple studies adjusting for fever/infection and continuing to find an APAP-ADHD link, and 5) the data failing to show that pain or NSAIDs confound the APAP-ADHD link together eliminate my concern about confounding by indication.

Genetic confounding

In addressing the very concerning matter of genetic confounding, first, we must ask whether genetics relates to both the outcome and the exposure. Surely, fever meets this requirement for the definition of a confounder as it is an indication for APAP use and is suspected (albeit as noted above, based on limited data) to elevate ADHD risk. Clearly, genetics contributes to ADHD risk as well. Leppert (2019)'s finding of an association between genetic risk score for ADHD and prenatal APAP supports the notion that genetics could be a true confounder. However, during the third trimester critical window for APAP toxicity, the association was small (late pregnancy, RR 1.11, 95% CI 1.04–1.18). Ricci (2023) demonstrated that to explain the entirety of the observed association between APAP and ADHD, a confounder would need to be on the order of a RR of approximately 3.0. Thus, it is unlikely that such a small confounding effect would *eliminate* the APAP-ADHD relationship. More directly, although Leppert's analysis raises a theoretical concern about the potential for genetic confounding, the authors state, "to draw conclusions about causality, future studies need to account for potential genetic confounding and triangulate evidence from different causally informative approaches."

Stergiakouli and Ruisch did just that. (Stergiakouli 2016, Ruisch 2018, reviewed above) Both adjusted for risk score within the same database (ALSPAC) that Leppert used in reporting his finding, and neither found any substantial impact on the APAP and ADHD relationship. Thus, within the ALSPAC study, the theoretical concern of confounding by ADHD genetic risk score did not bear out.

As the Court noted, "researchers can attempt to control for genetic confounders by gathering data on parental ADHD diagnoses, using negative control exposures, or conducting sibling control studies." (Order at 21) These are approaches that several authors have taken.

The approaches used to mitigate genetic confounding were as follows. Many studies adjusted for parental ADHD diagnosis and/or other psychiatric conditions in their analyses. (Liew 2016, Alemany 2021, Masarwa 2020, Chen 2019, Ystrom 2017, Inoue 2021) Sibling designs were used by Gustavson et al. (2021) and Brandlistuen (2013). Negative controls were studied by Ystrom (2017), Liew (2019), and Inoue (2021). Ystrom (2017), Guvstavson (2021) and Baker (2020) used propensity matching. Leppert, Ruisch, and Stergiakouli assessed genetic risk scores for ADHD in relation to APAP use.

The reviews of the Brandlistuen, Ruisch and Stergiakouli studies are studies that I did not include in my primary Bradford Hill analysis, but did consider for context. To briefly summarize their results, Brandlistuen found that within same sex sibling pairs, long duration (>28d) prenatal APAP use was associated with several ADHD behaviors on the order of risks of 1.5 to 1.7. This suggested that after sibling adjustment for genetic confounding, long-term exposure resulted in increased risk. (Brandlistuen 2013) Ruisch reported higher oppositional defiant symptom scores reported by mothers of children born after prenatal use of APAP (RR=1.24, 98.3% CI 1.05–1.47), a finding that correlated highly with teacher ratings (P=0.002). This was after adjustment for genetic score. That is, the relationship held after genetic risk score adjustment. Stergiakouli found no evidence of ADHD behavioral risk associated with maternal postnatal use or paternal use. The authors also found that ADHD polygenic risk scores were not associated with APAP use at 18 weeks or 32 weeks of pregnancy. That is, there was no indication that the genetics confounded the association between APAP use and ADHD behaviors. Stergiakouli's finding of no association between paternal APAP use and a behavioral measure of ADHD failed to replicate the finding by Ystrom (2017).

Many of the studies I did use to establish Hill's tenets have adjusted for parental evidence of ADHD and/or other psychiatric diagnoses including scores on psychological tests, self-reports,

or medication use. (Liew 2016, Alemany 2021, Masarwa 2020, Chen 2019, Ystrom 2017). After such adjustments, all continued to show statistically significant positive associations.

Sibling designs limit genetic effects as well as shared familial exposures. However, they do not exclude genetic nor familial aggregation. Siblings share only 50% of their genes. Moreover, it is quite possible that mothers of children who have developed symptoms of ADHD might avoid taking any medications, including analgesics in the next pregnancy and may change other pregnancy and post-natal behaviors to limit any possible adverse exposures. Thus, siblings would not share all pertinent environmental factors. Finally, epigenetic effects not shared by siblings (genetic alterations that do not relate to the genetic code of the mother or father but occur after conception), might be an important aspect of the genetics of ADHD. This is a likely explanation for the fact that first births are more likely to be affected by ADHD than subsequent births. Use of siblings as controls would not overcome this issue. Thus, sibling studies limit but do not exclude shared familial confounding.

Gustavson (2021) used a sibling design. If its results were replicated, that would be a cause for greater concern about genetic confounding in showing that within families (sibling pairs), the relationship between prenatal APAP use and ADHD was almost eliminated. However, because it was powered primarily by only 34 informative sibling pairs, this result had limited precision (HR 1.06, 95% CI 0.51–2.05). The authors themselves note, “the finding of similar risk for ADHD in siblings discordant for long-term maternal acetaminophen use must be interpreted with caution and needs to be replicated in other studies.” The authors also acknowledge that sibling designs may underestimate true risk. “The sibling comparison model adjusts not only for stable confounding factors, but also for potential mediating factors that affect all siblings even if only one is exposed (Sjolander & Zetterqvist, 2017). This may lead to underestimation of association estimates.” In contrast to Gustavson’s findings, Brandlistuen (2013) found no evidence of

genetic confounding in a sibling control design using 2,919 same-sex sibling pairs. Because of the larger sample size, Brandlistuen was able to examine the more informative group of those with longer duration exposure, though admittedly it did not employ ADHD diagnoses as its endpoint. What it does demonstrate is the value of a larger sample to bolster confidence in a result.

Ystrom (2017) and Baker (2020) used propensity score adjustment to limit unmeasured confounding including genetic factors. Both showed statistically significant associations between APAP and ADHD despite such adjustment.

Postnatal/prenatal NCE designs did not support genetic confounding. Ystrom (2017), Liew (2019), and Inoue (2021) looked at maternal APAP use in the postnatal and/or prenatal period. None found such use to be associated with elevated ADHD risk. Somewhat concerningly, the Ystrom (2017) study showed that paternal APAP use was associated with ADHD. Although that result is unexpected, it does not support the hypothesis of genetic confounding. Whatever is driving that unexpected outcome, it is not the mother's genetics. It seems to me that a better NCE to include/exclude genetic confounding is a mother's own use outside of the pregnancy period, and that kind of association with ADHD was not demonstrated by Ystrom *or any other* author.

Because of Gustavson, I continue to hold the concern that genetic confounding may *partially* inflate the observed risk between maternal APAP use and ADHD risk at least to some extent. However, I can find no compelling data in the literature to date to support the idea that genetics could *eliminate* the association. Twelve studies carefully examined the possibility of confounding by genetics. The results from three of those studies raised concerns about genetic confounding that are worth taking seriously (Ystrom 2017, Gustavson 2021, Leppert 2019). But these studies

were either small and imprecise (Gustavson 2021), or showed an effect too modest to account for the APAP-ADHD relationship and did not play out in other studies, (Leppert 2019) or conflicted with the negative NCE post-natal maternal results from the same study (Ystrom 2017). Thus, I am not swayed that genetic confounding, more likely than not, explains away the compelling evidence of causality.

As noted above, I have relied on studies employing diagnostic endpoints when evaluating the Bradford Hill criteria and included a discussion of studies employing non-diagnostic endpoints for context only. Although I have discussed how some of those studies further bolster the case against bias and confounding explaining the entirety of the observed associations, it is worth pointing out explicitly that I believe causation (rather than bias, chance, or confounding) is the most likely explanation even if one were to blinker one's view to the set of diagnostic-endpoints studies alone.

Chance is extremely unlikely, given the number of diagnostic-endpoint studies and the fact that most of the results are statistically significant. There are too many results to be explainable by chance. As explained in detail above, any bias (most notably exposure misclassification) likely runs toward the null and thus understates the true risk, as evidenced by the Baker and two Ji studies, which saw an *increase* in observed risk after employing biomarker measurements of exposure. Finally, confounding by indication or genetics—though a possibility to be taken seriously—is not the most likely explanation even looking at studies using diagnostic endpoints. As for confounding by indication, some of the diagnostic-endpoint studies explicitly controlled for indication and saw minimal change in results. (Liew 2014, Ystrom 2017, Ji 2018, Ji 2020). As for confounding by genetics, although Gustavson (2021) is cause for concern, and the paternal result from Ystrom is indeed odd, as explained above, Gustavson has serious limitations, most notably its small size, and the Ystrom *paternal* result (again, though odd) does not suggest

anything about confounding by *maternal* genetics. In my view, the maternal negative control results from Ystrom and Liew 2019 suggest that confounding by genetics is not the most likely explanation. As a result, in my opinion, even looking at the limited subset of studies that employed diagnostic endpoints, causation is the most likely explanation for these results. It is of course true that the studies relying on non-diagnostic endpoints further strengthen the case against bias, chance, and confounding—and in favor of causation—but they are not necessary to reach a causal inference.

Statistical significance

In this report, reference to statistical significance was made for completeness but it was not used as a measure of impact or import. It was also not employed as a means of excluding or including studies in assessing strength of association. Such avoidance in relying on statistical significance is consistent with accepted practice in epidemiology. Statistical significance depends on sample size and any particular cut-off is arbitrary. Any of the numbers found within a 95% confidence interval are ones that may have been determined to represent the degree of association in 95 cases if one were to have repeated the observation 100 times. This means that two estimates with overlapping confidence intervals are generally not statistically different. For instance, in dose-response results, if the point estimate rises and the test of trend is significant, this suggests a meaningful trend. Just because each number in the series is consistently greater than the last does not negate the trend.

Statistical significance is not a means of excluding the importance of a positive study in contributing to consistency of association. Hill's approach was to consider the body of evidence together and with all its subtlety to arrive at a conclusion of causality. However, it is worth

noting that there are a large number of statistically significant results in this literature, as the forest plot shown above makes clear.

The key to establishing causality is finding a clinically meaningful, consistent, temporal relationship between increasing exposure and disease that is biologically plausible after considering all of the literature in aggregate. A single study does not make or break the case. Effects found in some studies can contribute to the case for causality even if they are not, alone, statistically significant.

Review of statements from medical organization and professional societies.

The Court pointed to a variety of statements from published authors and medical organizations that have expressed skepticism or agnosticism about whether the associations observed between prenatal APAP exposure and ADHD are causal. The Court criticized previous experts for "disregarding relevant reviews of epidemiological studies conducted by medical and governmental associations." (Order at 105) I have considered the published skeptical concerns with all due respect, concern, and consideration.

Several professional societies responded adversely to the Bauer consensus publication, but they did so in the absence of conducting systematic reviews. European and Canadian professional societies (European Network of Teratologic Information Services or ENTIS and Society for Gynecology Canada or SOGC) both questioned the case for causality, citing "weak evidence." However, this was not a refutation of the call for precautionary action. It was, instead, a questioning of causality in the absence of their own complete review of the data. In contrast, the primary American professional society to weigh in was ACOG. In response to the consensus statement in 2021, ACOG stated, "[t]his consensus statement, and studies that have

been conducted in the past, show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues." Note the language, "prudent use." In other words, although seemingly opposing the consensus statement, the society's stance actually agreed that caution should be used in the use of prenatal APAP. Beyond that, ACOG did not conduct a systematic review of Hill's tenets to assess causality, as I did here.

As an expert in this case, my opinion focuses on the question of causality. However, personally, regarding benefit vs. risk of prenatal APAP use, I agree with both Bauer and ACOG in recommending caution. I believe that APAP use should be available to women experiencing short-term fever and mild to moderate short-term pain during pregnancy, the very uses for which it is labeled and recommended by manufacturers. However, women should be made aware of the evidence regarding longer term prenatal APAP use and with this knowledge they, in concert with their healthcare provider, should determine how best to use APAP during pregnancy.

In addition to the skepticism expressed by these organizations, I considered the following.

FDA

I have assessed the various reviews that scientists within the FDA have performed with respect to APAP and neurodevelopmental disorders. The FDA agreed that there is an association for ADHD, indeed a consistent association for ADHD. Although the FDA pointed to various limitations in the literature, the FDA nowhere explains why causation is still not the most likely explanation for the association, even if it is not the only possibility. Nor did FDA perform a Bradford Hill analysis, as I have here.

Society for Maternal-Fetal Medicine (SMFM)

The opinion of SMFM was published in 2017, before several of the most important studies reviewed above. Both the Ji and Baker studies explicitly state that their studies were designed to address the shortcomings—in particular exposure assessment—identified by SMFM. Ji 2020 ("This study aimed to address the limitations highlighted by the SMFM, FDA, and AAP in relevant previous studies"). Baker 2020 ("Owing to limitations of prior studies, the US Food and Drug Administration and the Society for Maternal-Fetal Medicine have not changed their recommendations to reflect the potential harm of prenatal acetaminophen to neurodevelopment. The Society for Maternal-Fetal Medicine cited maternal self-report of acetaminophen use, lack of quantification of acetaminophen dose, and measurement of outcomes using questionnaires as 3 limitations of previous studies. A recent study in the Boston Birth Cohort addressed these limitations by finding a positive association between acetaminophen metabolites measured in cord plasma and physician diagnosis of ADHD."). The Ricci 2023 meta-analysis also post-dates the SMFM statement by many years. Aside from their now-dated review of the literature, SMFM suggests that "the weight of the evidence is inconclusive regarding a possible causal relationship," but nowhere explains why causation is not the most likely explanation. Nor did SMFM perform a Bradford Hill analysis, as I have here.

Royal College of Obstetricians and Gynecologists (RCOG)

In 2018, before more than five years' worth of subsequent studies, the Royal College published a single paragraph declaring that although "some studies have demonstrated associations between the use of paracetamol antenatally and adverse outcomes for the offspring" including "behavioral problems"—citing Liew (2014)—"[c]urrent advice is that paracetamol remains safe for use during pregnancy and breastfeeding." In addition to being dated, the Royal College did not appear to perform an exhaustive literature review. Despite acknowledging the associations, they nowhere explain why causation is not the most likely explanation.

Addressing the limitations expressed by study authors

The Court expressed concern about "exceeding the limitations" placed on studies by the study authors themselves. As a result, I have quoted extensively from the authors' own interpretations of their results. Given the volume of the literature, it is impossible to quote every caveat here, but I have endeavored to address as many of them from the studies as possible. I have also attempted to document and assess all the strengths and weaknesses of individual studies. Finally, I have considered with great concern the issues of bias, confounding, and small effect sizes expressed by skeptical authors. I do not believe that any of these considerations is more likely than not the explanation for the association between prenatal APAP use and ADHD.

I entirely agree with study authors who, for their individual studies, have expressed caution about residual confounding. The Reference Manual cautions, "Generally, researchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn." (Federal Reference Manual at 599) I do not, however, agree that "more studies are *needed*," which, I believe, expresses more caution than warranted before deciding that an exposure meets the standard of more likely than not causal. Given the totality of the evidence, I believe it is possible in the absence of further observational studies to reach my conclusion about causation. The individual study authors, who were not performing a Bradford Hill analysis, are not in a position to conclude whether more studies are actually needed based on the totality of the evidence.

My conclusions are based on my review of the entirety of the literature to the present day, a task (to my knowledge) that no professional society or agency has attempted. I am also not aware of any study (besides the Alemany meta-analysis) that performed a complete or partial Bradford Hill analysis—the classic method of deciding whether an association is causal. (Alemany 2021)

The Alemany meta-analysis determined that five of the Bradford Hill criteria were satisfied—consistency, coherence, biologic plausibility, temporality, and dose response. These are criteria for which I concluded that Hill's tenets were met. Alemany expressed no opinion on specificity, strength, or analogy. Strength of Association I considered to be partially met. Specificity per my assessment was not met. Experiment was not met. I deemed analogy to be met on the basis of comparison to valproic acid, which Alemany did not address. In the Court's order, the Court noted that Alemany (2021) "briefly mentioned the Bradford Hill factors by citing to other research." (Order at 69). Although the Alemany authors' Bradford Hill analysis was not as extensive as mine has been here, it is no surprise that they cited to other research. Bradford Hill is about considering the literature as a whole, rather than the results of a single study. It would be a rare situation indeed in which a Bradford Hill analysis could be conducted without citing to other research.

Final Summary and Conclusion Regarding General Causation

- Acetaminophen exposure during pregnancy was associated with RRs typically in the range of 1.2 to 1.6. For measures of biologic exposure, the risk was stronger (RRs 2.44–2.86). Nonetheless, to be conservative, I consider the risk modest. The Ricci meta-analysis characterized the associations as "small to moderate."
- For long duration users, the risk was more pronounced (RR 1.78–2.20).
- Many previously established causes of disease are within the 1.2 to 1.6 observed risk range, the same range found for prenatal APAP and ADHD risk.
- The positive association (in terms of risk estimate, not statistical significance) between APAP use in pregnancy and ADHD is consistent independent of population, time frame, design of the cohort, approach to measurement, and statistical handling of the data.

- APAP toxicity appears to have a specific sensitive window which is the third and possibly second trimester and this concords with current knowledge of when ADHD develops in the fetal brain.
- Studies that considered dose-response found a higher risk among the most exposed APAP users. This was true for duration, frequency, and for concentration in meconium/cord blood/maternal blood.
- There are biologically plausible pathways for APAP toxicity, including those mediated by inflammation and/or oxidative stress.
- Systematic bias from confounding by indication and confounding by genetics, as well as unmeasured confounding, in my estimation, is unlikely to account for the APAP-ADHD relationship. Ricci (2023) provided convincing evidence against confounding by indication, as did other authors. Confounding by genetics was considered in 12 studies, 3 of which raised important concerns. However, these I considered too small and imprecise (Gustavson (2021)), too modest in effect size to account for the APAP-ADHD relationship (Leppert (2019)), or inconsistent in the same study with a superior NCE indicator, (Ystrom (2017)). Meanwhile, numerous studies have adjusted for factors related to genetics such as parental ADHD risk, have shown that maternal NCEs did not show any association between APAP prenatal use and ADHD, and have shown no evidence of APAP exposure among non-affected siblings. Thus, I am not swayed that indication or genetic confounding explain the APAP-ADHD relationship.
- Overall, the association between prenatal APAP use and ADHD is coherent. That is, the association does not “seriously conflict” with generally known facts about biology.
- I conclude that Hill’s elements of consistency, dose-response, temporality, analogy, biologic plausibility, and coherence are met. I conclude that strength of association is partially met. I conclude that specificity and experiment are not satisfied. As noted, it is

not necessary that every tenet be met. The only absolutely requisite tenet is temporality, which was met. As detailed above, the tenets carrying the most weight were met. Based on the above data, discussion, and considerations, it is my expert opinion that, within a reasonable degree of scientific certainty, prenatal use of APAP causes ADHD.

February 7, 2024

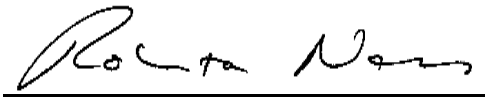


Exhibit B

Materials Considered List:
Roberta B. Ness, MD, MPH

"ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy," 2021. https://www.acog.org/en/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy.

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Exhibit C

CURRICULUM VITAE

NAME:	Roberta B. Ness, M.D., M.P.H.
CITIZENSHIP:	US
CONTACT INFORMATION:	James W. Rockwell Professor of Public Health The University of Texas School of Public Health 1200 Herman Pressler, E1015 Houston, TX 77030 713-500-9052 713-500-9442 *fax* Roberta.B.Ness@uth.tmc.edu

EDUCATION AND TRAINING

Undergraduate

1976-1980	University of Maryland, MD Honors College	B.Sc.	Microbiology

Graduate

1980-1984	Cornell University, NY	M.D.	Medicine
1987-1989	Columbia University School of Public Health New York, NY	M.P.H.	Epidemiology

Post-Graduate

1984-1985	Bellevue Hospital/NYU New York, NY	Internship	Saul Farber, M.D.
1985-1987	Bellevue Hospital/NYU New York, NY	Resident	Saul Farber, M.D.
1988-1990	Columbia University School of Public Health New York, NY	NIH Training Fellowship	Jennifer Kelsey, Ph.D.

APPOINTMENTS AND POSITIONS

Academic

1988-93	University of Pennsylvania Department of Psychiatry	Clinical Associate
1990-93	University of Pennsylvania Department of Medicine	Assistant Professor
1991-93	University of Pennsylvania Clinical Epidemiology Unit	Core Faculty
1993-98	University of Pittsburgh Graduate School of Public Health Epidemiology	Assistant Professor

1994-2008	University of Pittsburgh, School of Medicine Department of Obstetrics &/Gynecology	Secondary Appointment
1995-2008	University of Pittsburgh, School of Medicine Department of Medicine	Secondary Appointment
1995-2008	University of Pittsburgh Graduate School of Public Health Epidemiology of Women's Health Program	Founding Director
1997-2008	University of Pittsburgh Cancer Institute Cancer Epidemiology Program	Director
1998-2002	University of Pittsburgh Graduate School of Public Health Epidemiology	Associate Professor with tenure
2000-08	University of Pittsburgh Schools of Health Sciences Bridging the Gaps Internship Program	Founder; Advisory Board
2002-08	University of Pittsburgh Women's Studies Program	Secondary Appointment
2002-08	University of Pittsburgh Graduate School of Public Health Epidemiology	Professor with tenure
2003	University of Pittsburgh Graduate School of Public Health	Associate Dean for Research
2003-08	University of Pittsburgh Graduate School of Public Health Department of Epidemiology	Chair
2005-06	University of Pittsburgh Graduate School of Public Health	Interim Dean
2008-14	The University of Texas School of Public Health	Dean
2008-14	The University of Texas School of Public Health	M. David Low Chair in Public Health
2009-	The University of Texas Health Science Center at Houston Medical School Department of Internal Medicine	Secondary Appointment Professor

2009-	The University of Texas Health Science Center at Houston Medical School Department of Obstetrics & Gynecology	Secondary Appointment Professor
2009-	University of Pittsburgh, Graduate School of Public Health, Department of Epidemiology	Adjunct Professor
2009-	The University of Texas M.D. Anderson Cancer Center	Adjunct Professor
2010-	The University of Texas School of Public Health, Center for Innovation Generation	Founding Director
2011-17	The University of Texas Health Science Center at Houston	Vice President for Innovation
2014-2019	The University of Texas School of Public Health	James W. Rockwell Professorship in Public Health (Preventive Medicine and Epidemiology)

Non-Academic

1990-93	Hospital of the University of Pennsylvania	Attending Physician Emergency Department
1994-96	Magee-Womens Hospital Pittsburgh, PA	Attending Physician Emergency Department
1996-99	University of Pittsburgh Medical Center Department of Medicine	Attending Physician

CERTIFICATION AND LICENSURE

Specialty Certification

Certificate	American Board of Internal Medicine	1987

Medical or Other Professional Licensure

Medical licensure	New York	1985-88
Medical licensure	Pennsylvania	1988-2008

HONORS

1976	It's Academic College Scholarship
1980	B.Sc. With Honors Phi Beta Kappa Summa Cum Laude Sklar Award for Outstanding Research Mortar Board Leadership Honorary University of Maryland
1988	Training Grant Fellowship National Institutes of Health
1996	PA Leadership Award: Outstanding Contributions to Reproductive Research Family Health Council
1996	Teacher of the Year Award Graduate School of Public Health, University of Pittsburgh
1998	Top 25 Women Doctors Pittsburgh Post-Gazette
1999	Top Research Paper Award Society for Epidemiologic Research
2004	Elected Member American Society for Clinical Investigation
2004	Elected Member American Epidemiology Society
2005	Fellow American College of Physicians
2005	Fellow American College of Epidemiology
2006	Elected Member Delta Omega Honor Society
2006	Laureate Award American College of Physicians

2008	President American College of Epidemiology
2008	Distinguished Professor of Women's Health Society for General Internal Medicine
2008	Honoree in Technology and Innovation Women of Distinction Girl Scouts of America
2009	Elected Member Institute of Medicine, National Academies of Science
2009	Elected Member The Academy of Medicine Science and Engineering of Texas
2011	White House Appointment Mickey Leland National Air Toxics Research Center
2011	Elected Member Texas Philosophical Society
2012	President American Epidemiologic Society
2012	John Snow Award American Public Health Association
2012	Petersdorf Distinguished Lecture Association of American Medical Colleges Annual Meeting
2013	Nan Qiang University Lecture Xiamen University, China
2014	Board Member and Secretary The Academy of Medicine Science and Engineering of Texas
2014	Athena Swan Distinguished Lecture Oxford University, England
2014	Gaylord Anderson Distinguished Lecture University of Minnesota

2014	Julie Baker Memorial Lecture Roswell Park Cancer Center
2015	Leonard Schuman lecture, Graduate Summer Program 50th Anniv University of Michigan
2015	TEDMED talk 2015, Palm Springs
2015	Bill Nye (the Science Guy) Startalk Radio Show, featured scientist
2015	Perinatal Best Paper Award: Society for Pediatric Pathology
2016-18	TEDMED Editorial Advisory Board
2017	Lilienfeld Award, American College of Epidemiology
2018-	International Advisory Board, Norwegian Institute of Public Health
2018	Beasley Innovation Award, University of Texas
2018	Shephard Award Keynote, Centers for Disease Control, Atlanta
2018	Keynote speaker, Johns Hopkins Bloomberg School of Public Health 100th Centennial Celebration
2018	International Consultant Committee for Global Public Health (ICCGPH), China CDC
2022	Best Female Scientist Award Research.com

MAJOR SERVICE

Position	Type of Service	Agency	Year(s)
Member	Consensus Committee on Research in Pelvic Inflammatory Disease	National Institute for Allergy and Infectious Disease	1994
Chair	Committee on Women's Health	American College of Physicians	1996-8
Member	Panel on Reproductive Health	NIH Office of Women's Health Conference-Beyond Hunt Valley	1996-97
Member	Board of Directors	Pennsylvania Public Health Association	1996-98

Member	Data Safety/& Monitoring Committee STOP-DUB Trial	Agency for Healthcare Research and Quality	1997
Member	Advisory Board on Women's Health	Eli Lilly Company	1998
Member	Expert Panel on Cost-effectiveness for Chlamydia Screening	McMaster University	1998
Member	Tri-National Advisory Group on Preeclampsia	National Institute of Child Health and Development	1998
Member	Executive Committee: AIDS Training and Research Program	Fogarty AIDS International	1998-03
Member	Workshop on Hormone Replacement Therapy	Institute of Medicine National Academies of Science	1999
Member	Advisory Board: Women's Health Report Card	National Women's Law Center	1999-03
Member	Advisory Board: Oxford Collaborative Group on Cancers of the Genital Tract	Oxford University	2001-
Member	Scientific Advisory Panel	H.J. Heinz, International	2001-08
Member	Armed Forces Epidemiology Board	Department of Defense	2002-04
Co-Organizer	National Symposium on Ovarian Cancer and High-Risk Women	Funded by National Cancer Institute	2002
Advisor	Advisory Committee: Self-Testing for Sexually Transmitted Diseases	Centers for Disease Control and Prevention	2002
Member	Advisory Board	Fred Hutchinson Cancer Center SPORE	2002-04
Standing Member	ECD-1 Study Section	NIH Center for Scientific Review	2003-05
Member	Advisory Board	Centers for Disease Control/ Research, Triangle Institute: Ovarian Cancer Prevention Program	2003-05
Member	Advisory Committee: Rural Public Health Research	HRSA: Office of Rural Health Policy	2003
Member	Board of Directors	American College of Epidemiology	2004-10
Chair	Policy Committee	American College of Epidemiology	2004-07

Member	Committee on the Role of Asbestos in Causation of Gastrointestinal Cancers	Institute of Medicine National Academies of Science	2005
Standing Member	Infectious Disease and Reproduction Panel (IRAP)	NIH Center for Scientific Review	2005-08
Member	Advisory Board	Endometriosis Association	2005-08
Member	STD Treatment Guidelines Update Advisory Committee	Center for Disease Control	2005
Founder	Committee of Chairs	Departments of Epidemiology, North America	2005-08
Chair	Leadership Workshop on Rare Tumors – Ovarian Cancer Panel	National Cancer Institute	2005
Member	Advisory Committee: Directions in Research on Mitochondrial DNA	National Cancer Institute	2006
Member	Committee on the Impact of HIPAA on Biomedical Research	Institute of Medicine National Academies of Science	2007
Member	Advisory Committee: Chlamydia Immunobiology	Center for Disease Control and Prevention	2007-8
Founder	Joint Policy Committee, Societies of Epidemiology	Fourteen Societies of Epidemiology	2007
Host	Annual Meeting	American Society of Epidemiology	2008
Member	Advisory committee: Identifying Research Gaps in Bacterial Vaginosis	National Institute of Allergy and Infectious Disease	2008
Presentation	Workshop on Protecting Student's Records and Facilitating Education Research	National Academy of Sciences	2008
Member	Data Safety & Monitoring Committee Reproductive Medicine Network	National Institute of Child Health and Development	2008-10
Member	Executive Committee, National Children's Study	National Institute of Child Health and Development	2008-9
Member	Integration Panel	Department of Defense Ovarian Cancer Research Program	2008-10
Member	Board of Scientific Counselors	National Institutes of Environmental Health Sciences	2008-10

Member	Committee on Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease	Institute of Medicine National Academies of Science	2009-10
Member	Advisory Committee	Cancer Prevention and Research Institute of Texas	2009 -
Member	Consensus Panel on Colorectal Cancer Screening	National Institutes of Health	2009-10
Honorary Co-Organizer	Annual Dean's Retreat	Association of Schools of Public Health	2010
Chair	Committee on Blue Water Navy Vietnam Veterans and Agent Orange Exposure	Institute of Medicine National Academies of Science	2010-11
Member	Committee to Review the Federal Response to the Health Effects from the Gulf of Mexico Oil Spill	Institute of Medicine National Academies of Science	2010-
Member	Board of Directors	Association of Schools of Public Health	2011-14
Member	Committee on Preventative Services for Women	Institute of Medicine National Academies of Science	2011
Member	Board of Directors	National Board of Public Health Examiners	2011-14
Member	Committee on Science, Technology and the Law	National Academies of Science	2012-
Honorary Co-Organizer	Annual Dean's Retreat	Association of Schools of Public Health	2013
Consultant	GoMRI Research Board	BP Oil Spill Fund	2013
Consultant	Oil Spill Fund Board	National Academies of Science	2013
Member	Advisory Board, Innovation Institute	Texas Medical Center	2014
Member	Womens Health Leadership Summit	Cedar Sinai Medical Center	2014
Secretary	Board of Directors	The Academy of Medicine Engineering and Science of Texas	2014
Chair	Workshop on Genomics to the Investigation of Cancer Clusters	National Academy of Medicine	2022-3

EDITORIAL BOARDS

2003-	Editorial Board Sexually Transmitted Diseases Website World Health Organization
2004-	Editorial Board Annals of Epidemiology
2005-	Associate Editor American Journal of Epidemiology
2008-	Editorial Board Infectious Diseases in Obstetrics and Gynecology
2008	Editorial Board Journal of Inflammation Research
2008	Honorary Editorial Board Obesity Insights
2009	Editorial Board Journal of Pregnancy
2009-	Editorial Board Jornal of Clinical Epidemiology
2011	Editorial Board International J. of Privacy and Health Information Management
2015	Editorial Board Journal of Epidemiology and Public Health Reviews

TEACHING as PRIMARY INSTRUCTOR

University of Pittsburgh

Number	Title	Credits
Epid 2720	Environmental Causes of Reproductive Failure	2
Epid 2710	Epidemiology of Women's Health	2
	Summer Community Internship Program	0
Epid 2250	Departmental Seminar Series	1
Epid 2170	NIH Grant Writing	2

University of Texas

Epid 2166	Innovative Thinking	3
PH 5998	Capstone Course	3
PH 2720	Epidemiology Proposal Development	3
PH 2712	Experimental Methods in Epidemiology	3
PH 2999	Independent Study	2

RESEARCH

Grants and Contracts: Principal Investigator

Years Inclusive	Grant or Contract Title	Source and Number	Amount
1991-93	Parity and serum lipids in white and hispanic women.	National Heart Lung and Blood Institute, R03HL046168	$99,914
1993-98	Oral contraceptives and ovarian cancer	National Cancer Institute, R01CA63748	$2,184,540
1994-95	Women's health action agenda	Jewish Healthcare Foundation of Pittsburgh	$7,500
1995	Focus on women's health seminar	GSPH-Center for Public Health Policy	$3,000
1995-96	Program in the epidemiology of women's health	Jewish Healthcare Foundation of Pittsburgh	$100,000
1995-98	Cocaine use and pregnancy outcomes in inner city women	National Institute on Drug Abuse, R01DA08252	$2,099,097
1995-00	Effectiveness of outpatient treatment for PID	Agency for Health Care Policy and Research, R01HS08358	$5,792,480
1996-01	Preeclampsia: convergence of fetal and maternal factors – Core and Project PI	National Institutes of Child Health and Human Development, P01HD30367	$8,726,943
1996-99	Ovarian cancer and phenothalein use	National Institutes of Environmental Health Sciences, R01CA63748-5-1	$25,000
1996-99	Epidemiology of women's health program-education and community outreach	McCune Foundation	$171,468

1997-98	Survey of women's career paths among Pennsylvania physicians	American College of Physicians	$12,500
1997-00	Mutagenicity of AZT in children of HIV-infected women – subcontract	National Institutes of Child Health and Human Development, R01HD33648	$1,387,303
1998-03	Douching, vaginal microbiology, and PID	National Institute of Allergy and Infectious Disease, R01AI44151	$3,422,976
2000-05	Home screening for chlamydia surveillance	Agency for Healthcare Policy and Research, R01 HS10592	$1,696,066
2000-01	Effectiveness of outpatient treatment for PID – Continuation	National Institutes of Allergy and Infectious Disease, R21AI48909	$299,200
2001-05	Effectiveness of outpatient treatment for PID – Renewal	National Institutes of Allergy and Infectious Disease, R01HS08358	$3,320,279
2001-06	Ob-Gyn fellowships in epidemiology and clinical trials – Co-PI	National Institutes of Child Health and Human Development, T32HD040673	$860,415
2002-06	Preeclampsia: mechanisms and post-pregnancy implications Program Project – Core PI	National Institutes of Child Health and Human Development, HDP0130367	$7,462,688
2002-07	Inflammation and ovarian cancer	National Cancer Institute RO1CA095023	$3,323,070
2004-07	Gynecologic disease program	Henry M. Jackson Foundation	$280,000
2004-08	Novel risk factors and potential early detection markers for ovarian cancer Program project - Overall PI; project PI	Department of Defense DAMD 17-02-1-0669	$1,606,642
2005-09	Pesticides and infant neuropsychological development - Co-PI	National Institutes of Environmental Health Sciences	$2,407,838
2005-10	Fetal growth restriction and maternal cardiovascular risk	National Heart Lung and Blood Institute	$3,219,707
2005-09	Infection, inflammation, and preeclampsia – Co-PI	National Institutes of Child Health and Development	$2,101,428
2007-08	HIPAA Survey, societies of epidemiology	National Academies of Science	$128,000
2007-09	Risk markers for endometriosis among active duty women in the U.S. military	Department of Defense	$69,300

2007-12	Training grant in reproductive, perinatal, and pediatric epidemiology	National Institutes of Child Health and Development	$1,727,635
2007-12	National Children's Study (NCS)	National Institute of Child Health and Development - HHSN2672007000029C	$24,742,884
2006-11	Center for Clinical and Translational Sciences – co-PI	National Institutes of Academic Medical Science (NIH)	$7,224,045
2010-11	Innovation thinking Dissemination	The University of Texas System	$100,000
2010-11	Pioneer Award for Innovation Thinking Dissemination	The University of Texas Health Science Center at Houston	$50,000
2010-14	Collaborative Training of a New Cadre of Innovative Cancer Prevention Researchers	Cancer Prevention Research Institute of Texas	$3,600,780
2012-17	Center for Clinical and Translational Sciences (renewal) – co-PI	National Institutes of General Medical Science (NIH)	$20,000,000
2014-16	Collaborative Training of a New Cadre of Innovative Cancer Prevention Researchers (renewal)	Cancer Prevention Research Institute of Texas	$1,700,000
2016-21	Collaborative Training of a New Cadre of Innovative Cancer Prevention Researchers (renewal)	Cancer Prevention Research Institute of Texas	$4,000,000

Grants and Contracts: Co-Investigator

Years Inclusive	Title	Source and Grant or Contract Number	Amount
1992-97	Cancer clinical epidemiology training grant	National Institutes of Health, T32CA009679	$283,070
1991-92	Serum progesterone in the timely diagnosis of ectopic pregnancy	University of Pennsylvania Research Foundation Grant	$4,950
1992-03	Education programs in cancer prevention	National Cancer Institute, R25CA057703	$103,629
1994-01	Comparison of raloxifene HCI and placebo treatment of postmenopausal women with osteoporosis	Eli Lilly Company	$2,615,408
1995-98	Lead exposure, attention deficit disorder and delinquency	National Institute of Environmental Health Sciences, R01ES005015	$755,661
1996-98	Centers for Excellence in Women's Health	Health and Human Services	$247,436

1996-00	Lifestyle factors affecting fetal somatic mutation	National Institutes of Child Health and Human Development, R01HD033016	$1,515,926
1998-99	Program for healthcare to underserved populations	Corp. for National Service	$150,000
1998-02	Domestic violence and spontaneous abortion	National Institute for Mental Health, R01HD036918	$12,308
1998-00	Bone lead levels and college achievement scores	National Institutes of Environmental Health Sciences, R01ES009006	$210,000
1998-02	Molecular genetic studies of recurrent pregnancy loss	National Institutes of Child Health and Human Development, R01HD038126	$1,250,264
1998-02	Attention deficit disorder and exposure to lead	National Institutes of Environmental Health Sciences, R01ES05015-09	$742,427
1999-03	Pharmacogenetic determinants of fetal somatic mutation	National Institutes of Child Health and Human Development, R01HD36880-02	$1,097,925
1999-03	Alcohol use disorders and STDs among youth – Mentor	NIAAA, K23AA000303-01	$513,309
2000-03	Ovarian cancer risk and survival in BRCA carriers	Department of Defense, DAMD17-00-1-0569	$445,319
2000-05	Preventive oncology career award - Mentor	National Cancer Institute, K07CA080668	$661,791
2001-04	Bacterial vaginosis and spontaneous abortion	National Institutes of Health, R01HD38856	$350,347
2001-06	UPCI cancer education and career development program: T32 - Mentor	National Cancer Institute	$1,686,980
2002-07	Building interdisciplinary research careers in women's health – Mentor/Executive committee	National Institutes of Health	$2,500,000
2003-08	Optimal strategies for PID prevention and management: K07 – Mentor	Agency for Healthcare Research and Quality	$616,877
2004-09	Multidisciplinary Clinical Research Programs: K12 – Mentor/Executive committee	National Institutes of Health	$1,073,138
2005-08	*Mycoplasma genitalium* and pelvic inflammatory disease	National Institutes of Allergy and Infectious Disease	$892,250

2006-11	Contraceptive services / primary care to prevent birth defects: K23 – Mentor	National Institutes of Child Health and Development - K23 HD05185	$608,730
2006-10	Treatment of screened bacterial vaginosis: STD Prevention Network	National Institutes of Allergy and Infectious Disease	$2,900,00
2010-	PRE-EMPT: International Consortium of Research on Preeclampsia: co-PI	Gates Foundation	$645,773
2018-22	Prospective Epidemiologic Study of Novel Etiologic Agents of Pelvic Inflammatory Disease	National Institute of Health	$21,879

Major Invited Lectureships (Past seven years only)

Stanford/UC Berkley Conference: Teaching Creative and Innovative Minds. Innovation education. February, 2013, San Francisco, CA.

Ground Rounds/Visiting Professorship. Governor's State University. Innovative Thinking. February, 2013. Chicago, IL

American Epidemiologic Association meeting. Innovation Redesigned: Optimizing invention within the system of science. March, 2013. East Lansing, MI.

Leading Voices in Public Health Endowed Lectureship. East Tennessee U. Caution's erosion of the modern research university. March, 2013. Johnson City, TN

Grand Rounds. Southwestern Medical Center SWAT lecture. So you think you can innovate? March, 2013. Dallas, TX.

Grand Rounds. Roche Pharmaceuticals. Innovation and the modern pharmaceutical industry. April, 2013. Nutley, NJ.

Keynote. Columbia University School of Public Health Summit on Public Health Education. Promoting innovative thinking. June, 2013. New York City, NY.

Keynote. International Society for Hypertension in Pregnancy. Innovating in reproductive medicine. June, 2103. Tromso, Norway.

Keynote. Society of Medical Illustrators annual meeting. Creativity, art, and innovative thinking. July, 2013. Salt Lake City.

Grand Rounds. University of Maryland School of Public Health. So you think you can innovate? September, 2013. College Park, MD.

Grand Rounds. Methodist Hospital. Innovation in surgery. December, 2013. Houston, TX.

NanQiang Endowed University Lectureship. Xiamen University. Enhancing innovation in science. December, 2013. Xiamen, China.

Keynote. Texas Council of Academic Officers annual meeting. Innovation in higher education. January, 2014. Austin, TX

Keynote. Post-doc Day. University of Houston. Post-doctoral creativity. February, 2014. Houston, TX

Grand Rounds. UT Health Department of Surgery. Innovations in surgery. February, 2014. Houston, TX

Keynote. University of Pittsburgh Women in Science Conference. So you think you can innovate? April, 2014. Pittsburgh, PA.

Keynote. Ministry of Health, Uruguay. Innovation and public health. April, 2014. Montevideo, Uruguay.

Keynote. Medical College of Wisconsin. Community-based innovation. May, 2014. Milwaukee, WI.

Keynote. American Young Generation of Nuclear Scientists. Innovation and you. May, 2014. Phoenix, AZ.

Keynote. Northwestern U. Prevention Institute. So you think you can innovate? June, 2014. Chicago, IL.

Keynote and Visiting Professor. University of Southern California. Innovation lecture and workshop. September, 2014. Los Angeles, CA.

Keynote: Rice University/University of Houston Medicine, Engineering, Science, and Technology Conference. Innovation. September, 2014. Houston, TX.

Keynote: University of Irvine. Redesigning the System of Science. December, 2014. Irvine, CA

Julie Baker Memorial Lecture. University of Buffalo. The Creativity Crisis. December, 2014. Buffalo, NY.

Harvard University School of Public Health. Innovative thinking: The why and how. March, 2015. Boston, MA

AAAS Annual Science and Technology Policy Forum Annual Meeting. The Creativity Crisis Necessitates Redesigning the System of American Science. May, 2015. Washington, DC

Leonard M. Schuman lecture, Graduate Summer Program 50th anniversary. University of Michigan. Redesigning the System of Science. July, 2015. Ann Arbor, MI

Grand Rounds. University of Pittsburgh. The Future of Public Health: Recreating Us. September, 2015. Pittsburgh, PA

AMA Inspirations in Medicine Annual Meeting. The Creativity Crisis. October, 2015. Chicago, IL

Keynote: AAAS. How Geniuses Innovate. October, 2015. Washington, DC

TEDMED 2015. Recreate Yourself. November, 2015. Palm Springs, CA.

Bill Nye (the Science Guy) Startalk Radio show/podcast. November, 2015. Austin, TX

Keynote: Alliance for Continuing Education in the Health Professions Annual Conference. So you think you can innovate? January, 2016. National Harbor, MD.

Keynote: Association of Schools & Programs of Public Health. Identify and Encourage Innovative Research in Times of Austerity. March, 2016. Arlington, VA.

Keynote: Society of Biological Psychiatry Annual Meeting. Innovation in Science. May, 2016. Atlanta, GA.

Lewis Katz School of Medicine at Temple University. Commencement Address. May, 2016. Philadelphia, PA.

Keynote: Joint Policy Committee: Societies of Epidemiology. Congress of Epidemiology. Future of epidemiology. June, 2016. Miami, FL.

Collaboration with Chinese Academy of Science, Chinese Center for Disease Control and Prevention, and Institute of Microbiology Chinese Academy of Sciences. The Creativity Crisis. Beijing, China. August, 2016.

Keynote: Medical College of Wisconsin. Innovative Thinking. September, 2016.

Keynote: University of Pittsburgh Department of Epidemiology. Innovation in Epidemiology through Clinical Research Fall Seminar Series. October, 2016. Pittsburgh, PA.

Keynote: Mount Holyoke College Center for Leadership. "Imagination" Fall Series. January, 2017. South Hadley, MA.

Keynote: The University of Texas Health Science Center at Houston McGovern Medical School. Career Devlopment Seminar. March, 2017. Houston, TX.

Keynote: AAP, ASCI, and APSA Joint Annual Meeting. April, 2017. Chicago, IL.

Keynote: Gladstone Institute. April, 2017. San Francisco, CA.

Keynote: The University of Texas MD Anderson Cancer Center. Education Week. The Center for Innovation Generation and "Innovation in Education". May, 2017. Houston, TX.

Keynote: American Heart Association Reseach Leaders Academy. September, 2017. Denver, CO.

Keynote: Divison of Epidemiology and Community Health, School of Public Health, University of Minnesota. October, 2017. Minneapolis, MN.

Collaboration with Chinese Academy of Science & Chinese Translation of Book "*The Creativity Crisis"*. December, 2017. Beijing, China.

Speaker: University of Nebraska Medical Center (UNMC) and University of Nebraska at Omaha (UNO) Breakthrough Thinking Conference. April, 2018. Omaha, NE.

Keynote: Charles C. Shephard Award Ceremony Keynote. Centers for Disease Control, Atlanta. June, 2018.

Visiting Professorship. Multiple speaking engagements. Norweigian Institute for Public Health. April-June 2019.

Keynote: Vietnam National University. Hanoi, Vietnam. February 2020

Seminar: Community Partners International. Yangon Myanmar. January 2020

PUBLICATIONS

Refereed and Invited Papers

1. **Ness RB**, Price RA. (letter) An ecogenetic hypothesis for lung cancer. Arch Intern Med 1989; 149:1900.
2. **Ness RB**, Killian CD, Ness DE, Frost JB, McMahon D. Likelihood of contact with AIDS patients as a factor in medical students' residency choices.Acad Med 1989;64:588-94.
3. Price RA, Stunkard AJ, **Ness RB**, Wadden T, Heshka S, Kanders B, Cormillot A. Childhood onset (age <10) obesity has high familial risk. Int J Obes 1990;14:185-95.
4. Price RA, **Ness RB**, Laskarzewski P. Common major gene inheritance of extreme overweight. Hum Biol 1990;62:747-65.
5. Price RA, **Ness RB**, Sorensen TIA. Changes in commingled body mass index distributions associated with secular trends in overweight in Danish young men. Am J Epidemiol 1991;133:501-10.
6. **Ness RB.** Adiposity and age of menarche in Hispanic women. Am J Hum Biol 1991;3:41-7.
7. **Ness RB**, Price RA, Laskarzewski P. Inheritance of extreme overweight in black families. Hum Biol 1991;63:39-52.
8. **Ness RB**, Kelly JV, Killian CD. Housestaff recruitment to municipal and voluntary New York City residency programs during the AIDS epidemic. JAMA 1991;266:2843-6.
9. **Ness RB**, Kelly JV, Killian CD. (letter) Duty to attend upon the sick. JAMA 1992;267:1467-8.
10. Price RA, Lunetta K, **Ness RB**, Charles MA, Saad MF, Ravussin E, Bennett PH, Pettitt DJ, Knowler WC. Obesity in Pima Indians. Distribution characteristics and possible thresholds for genetic studies. Int J Obes 1992;16:851-7.
11. **Ness RB**. Bronchodilators added to inhaled corticosteroids. (editorial) ACP Journal Club 1993;118:48.
12. **Ness RB**. Effective education of patients with asthma who are allergic to dust mites. (editorial) ACP Journal Club 1993;118:14.
13. **Ness RB**, Kramer RA, Flegal KM. Gravidity, blood pressure and hypertension among white women in the Second National Health and Nutrition Examination Survey. Epidemiol 1993;4:303-9.
14. **Ness RB**, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, Stunkard AJ, D'Agostino RB. Number of pregnancies and the subsequent risk of cardiovascular disease. New Engl J Med 1993;328:1528-33.
15. **Ness RB**, Harris T, Cobb J. (letter) Gravidity and coronary heart disease. New Engl J Med 1993; 329:1894-5.
16. **Ness RB**. Estrogen and progestin for postmenopausal women: a meta-analysis. (editorial) ACP Journal Club 1993;118:65.

17. **Ness RB**, Schotland HM, Flegal KM, Shofer FS. Reproductive history and coronary heart disease risk in women. Epidemiol Rev 1994;16(2):298-314.
18. **Ness RB**. Race and survival after cardiac arrest. (editorial) ACP Journal Club 1994;120:47.
19. **Ness RB**, Grisso JA. Minority recruitment to clinical studies: How difficult is it? (editorial) SGIM Forum 1994;71:1.
20. **Ness RB**, Cobb J, Harris T. Does number of children increase the rate of coronary heart disease in men? Epidemiol 1995;6(4):442-445.
21. **Ness RB**, Cosmatos I, Flegal KM. Gravidity and serum lipids among Hispanic women in the Hispanic Health and Nutrition Examination Survey. J Wom Health 1995;4:149-59.
22. **Ness RB**. Parity, adiposity and body fat distribution among Hispanic women. Am J Hum Biol 1995;7:657-63.
23. **Ness RB**, Delaney K*, Rolfs RT, Gale JL. Practice variability in the inpatient treatment of pelvic inflammatory disease. J Wom Health 1995;4:531-9.
24. Soper D, **Ness RB**. Pelvic inflammatory disease and involuntary infertility: Prospective pilot observations. Infect Dis Obstet Gynecol 1995;3(4):145-8. PMCID: PMC2364436
25. **Ness RB**. Women's Health come to Pittsburgh. (editorial) Allegheny County Medical Society Bulletin. Fall, 1995.
26. Grisso JA, **Ness RB**. Update in Women's Health. Ann Intern Med 1996;123:737-4.
27. Berlin JA, **Ness RB**. Randomized clinical trials in the presence of diagnostic uncertainty: Implications for measures of efficacy and sample size. Controlled Clin Trials 1996;17:191-200.
28. **Ness RB**, Roberts J. Heterogeneous causes constituting the single syndrome of preeclampsia: A hypothesis and its implications. Am J Obstet Gynecol 1996;175:1365-70.
29. **Ness RB**, Keder LM*, Soper DE, Amortegui AJ, Gluck J, Wiesenfeld H, Sweet RL, Rice PA, Peipert JF, Donegan SP, Kanbour-Shakier A. Oral contraception and the recognition of endometritis. Am J Obstet Gynecol 1997;176:580-5.
30. D'Elio MA*, **Ness RB**, Matthews KA, Kuller LH. Are life stress and social support related to parity in women. Behav Med 1997;23(2):87-94.
31. **Ness RB**, Kuller LH. The study of women's health as a paradigm for understanding disease mediation. J Wom Health 1997;6:329-36.
32. **Ness RB**, Markovic N, Carlson CL*, Coughlin MT.* Do men become infertile after sexually transmitted urethritis: an epidemiologic analysis. Fertil Steril 1997;68:205-13.
33. **Ness RB**, Nelson DB*, Kumanyika SK, Grisso JA. Evaluating minority recruitment into clinical studies: how good are the data? Ann Epidemiol 1997; 7:472-8.
34. Grisso JA, **Ness RB**, Hendrix S. Update in women's health. Ann Int Med 1997; 127:1006-12.
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37. Sozio J*, **Ness RB**. Chlamydial lower genital tract infection and spontaneous abortion. Infect Dis Obstet Gynecol 1998;6:8-12. PMCID: PMC1784775
38. **Ness RB**, McLaughlin MT, Heine RP, Bass DC, Mortimer L. Fetal fibronectin as a marker to discriminate between ectopic and intrauterine pregnancies. Am J Obstet Gynecol 1998;179

39. Nelson DB*, **Ness RB**, Peipert JF, Soper DE, Amortegui AJ, Gluck J, Wiesenfeld H, Rice PA. Factors predicting upper genital tract inflammation among women with lower genital tract infection. J Wom Health 1998;7:1033-1040.

40. Powers RW, Evans RW, Majors AK, Ojimba JI, **Ness RB**, Crombleholme WR, Roberts JM. Plasma homocysteine is increased in preeclampsia and associated with evidence of endothelial activation. Am J Obstet Gynecol 1998;179:1605-11.

41. **Ness RB**. HRT is not associated with cardiovascular events or cancer in postmenopausal women in recent clinical trials. (editorial) ACP Journal Club 1998;126:48.

42. **Ness RB**, Grisso JA, Hirshinger N, Markovic N, Shaw L, Day N, Kline J. Cocaine exposure increases the risk of spontaneous abortion. N Engl J Med 1999;340:333-9.

43. **Ness RB**, Cottreau C.* Possible role of pelvic inflammation in ovarian cancer. J Natl Cancer Inst 1999;91:1459.

44. Powers RW, Minich LA, Lykins DL, **Ness RB**, Crombleholme WR, Roberts JM. Methylenetetrahydrofolate reductase polymorphism, folate and susceptibility to preeclampsia. J Soc Gyn Invest 1999;6:74-9.

45. Lain KY*, Powers RW, Krohn MA, **Ness RB**, Crombleholme WR, Roberts JM. Urinary cotinine concentration confirms the reduced risk of preeclampsia with tobacco exposure. Am J Obstet Gynecol 1999;181:1192-6.

46. Bigbee WL, Day RD, Grant SG, Keohavong P, Xi L, Zhang L, **Ness RB**. Impact of maternal lifestyle factors on newborn *hprt* mutant frequencies and molecular spectrum - initial results from the Prenatal Exposures and Preeclampsia Prevention (PEPP) Study. Mutation Res 1999;431(2);279-89.

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51. Peipert JF, **Ness RB**, Soper DE, Bass D. Association of lower genital tract inflammation with objective evidence of endometritis. Infect Dis Obstet Gynecol 2000;8(2):83-7. PMCID: PMC1784668

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57. **Ness RB**, Grisso JA, Klapper J, Vergona R. Racial differences in ovarian cancer risk. J Natl Med Assoc. 2000;92(4):176-82. PMCID: PMC2640605

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59. **Ness RB**, Buhari A, Gutai J, Kuller LH. Reproductive history in relation to plasma hormone levels in healthy post-menopausal women. Maturitas 2000;35:149-57.

60. Boyles SH*, **Ness RB**, Grisso JA, Markovic N, Bromberger J. Life events stress, social support and effects of spontaneous abortion. Health Psychol 2000;19:510-4.

61. Cooper GS, Longnecker MP, Sandler DP, Ness RB. Risk of ovarian cancer in relation to use of phenolphthalein-containing laxatives. Br J Cancer 2000;82(3):404-6. PMCID: PMC2374557

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63. Whiteman D, Murphy M, Cook L, Cramer D, Hartge P, Marchbanks P, **Ness RB,** et al. (letter) Multiple births and risk of epithelial ovarian cancer. J Natl Cancer Inst 2001;93:319-20.

64. **Ness RB**, Grisso JA, Vergona R, Klapper J, Schlesselman JJ, Morgan M, Wheeler JE. Oral contraceptives, other methods of contraception, and risk reduction for ovarian cancer risk. Epidemiology 2001;12:307-12.

65. Peipert JF, **Ness RB**, Blume J, et al. Clinical predictors of endometritis in women with symptoms and signs of pelvic inflammatory disease. Am J Obstet Gynecol 2001;184(5):856-63.

66. **Ness RB**, Soper DE, Holley RL, Peipert J, Randall H, Sweet RL, et al. Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) Study. Am J Obstet Gynecol 2001;185:121-27.

67. Powers RW, Evans RW, **Ness RB**, Crombleholme WR, Roberts JM. Homocysteine and cellular fibronectin are increased in preeclampsia, not transient hypertension of pregnancy. Hyper Preg 2001;20(1):69-77.

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71. Modugno FM*, **Ness RB**. Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness. Ann Epidemiol 2001;11(8):568-74.

72. Vine MF, **Ness RB**, Calingaert B, Schildkraut JM, Berchuck A. Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. Gyn Oncol 2001;83(3):466-71.

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Study. Am J Obstet Gynecol 2002;186:929-37.

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Exhibit D

Prior Testimony List (2020-2024)

- ***Matthey v. Johnson & Johnson et al.*** **(Federal court)**
- ***Sugarman v. Johnson & Johnson et al.*** **(Florida)**
- ***Seskin v. Johnson & Johnson et al.*** **(Florida)**
- ***Valadez v. Boehringer Ingelheim et al.*** **(Illinois)**
- ***Sterner v. Portercare Adventist Health System*** **(Colorado)**